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The Influence Of Gender And Aging On The Neural Circuitry Supporing Facial Emotion Processing In Adults With Major Depressive Disorder

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THE INFLUENCE OF GENDER AND AGING ON THE NEURAL CIRCUITRY SUPPORING FACIAL EMOTION PROCESSING IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

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DEDICATION

This dissertation is dedicated to my family. Without their unwavering support, this project would not have been possible.

To my parents, Dawn and Brian Anderson: Thank you for your unconditional support throughout my academic career. Thank you for encouraging me to pursue a career that I find fulfilling. You have always made me feel loved and supported, and have modeled integrity and a strong work ethic throughout my life.

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Finally, this dissertation is dedicated to all those whose lives are affected by depression.

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CHAPTER 1

INTRODUCTION

General Introduction

Major Depressive Disorder (MDD), among the most common psychiatric disorders, affects approximately 16% of adults in the United States over a lifetime (Kessler et al., 2003). One biological theory regarding its genesis posits that depression results from dysregulation of emotion processing circuitry. Supporting this theory, individuals with MDD have been demonstrated to exhibit decreased efficiency in their ability to process emotional stimuli, including the ability to recognize emotions in others' faces (Csukly, Czobor, Szily, Takacs, & Simon, 2009; Langenecker et al., 2005; Langenecker, Caveney et al., 2007). Functional neuroimaging studies have demonstrated disruption in the neural circuitry supporting emotion processing in depressed adults, affecting limbic (e.g., amygdala, hippocampal formation, Fu et al., 2004; Sheline et al., 2001; Surguladze et al., 2005), basal ganglia (Frodl et al., 2009; Surguladze et al., 2005), and various cortical regions (e.g., insula, fusiform gyrus, cingulate, frontal regions; Frodl et al., 2009; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Surguladze et al. 2005, Fu et al., 2004; Davidson, Irwin, Anderle, & Kalin, 2003).

Depression is approximately two times more prevalent in women than in men (Weissman et al., 1996). In healthy adults, women are more accurate at detecting emotions than men (Thayer & Johnsen, 2000) and gender differences in neural circuitry supporting emotion processing have been reported, such that women demonstrate greater activation of frontal and limbic regions (e.g., Aleman & Swart, 2008). In depressed adults, gender-specific decrements in facial emotion perception accuracy have been reported (Wright et al., 2009), such that depressed women were less accurate at detecting emotions than both healthy control women and depressed men, whereas

depressed men performed similarly to control men. Given that gender has been demonstrated to differentially affect emotion processing, and that women are more highly susceptible to MDD, it is surprising that gender is largely ignored in functional neuroimaging studies of facial emotion processing in MDD, even most recently (e.g., Costafreda, Khanna, Mourao-Miranda, & Fu, 2009; Frodl et al., 2009; Fu et al., 2008). Furthermore, unequal numbers of men and women are typically included in these studies (favoring women), rendering it unclear whether the results can be generalizable to both men and women with MDD.

Advanced age has also been demonstrated to be an important moderator of emotion processing. Healthy older individuals are less accurate at processing emotions than are healthy young adults (Calder et al., 2003; Sullivan & Ruffman, 2004). Furthermore, functional neuroimaging has demonstrated age-related alterations in the circuitry supporting recognition of emotional expressions, in which older adults demonstrate reduced activation of limbic regions (e.g., amygdala/hippocampus; Fischer et al., 2005; Gunning-Dixon et al., 2003; Iidaka et al., 2002) and greater cortical activation (e.g., insula, frontal cortex; Fischer et al., 2005; Gunning-Dixon et al., 2003).

Due to these age effects upon emotion processing in healthy adults, it is conceivable that advanced age may add an increased burden to extant emotion processing deficits in depressed adults. Surprisingly, few functional imaging studies of depressed elder adults have been conducted, and only one functional imaging study, to this author's knowledge, has examined neural bases of emotion processing in depressed elders. In this study (Brassen, Kalisch, Weber-Fahr, Braus, & Buchel, 2008), a group of late-onset depressed women demonstrated increased activation of the ventromedial prefrontal cortex in response to an emotional word judgment paradigm compared to their healthy control peers. As such, although early evidence suggests that

disruption in emotional processing circuitry continues into MDD in late life, the literature with regard to this disruption is sparse. No studies have examined emotion processing circuitry in elders with clearly defined early-onset MDD, and no studies have incorporated both men and women. Underscoring the need for these studies, age and gender each have been shown to be important determinants of decrements in face emotion processing accuracy in MDD (Wright & Langenecker, 2008). Specifically, women with MDD performed more poorly than healthy control women in both young and older age groups. In contrast, young men with MDD performed equivalently to young healthy control men, whereas older men with MDD performed more poorly than older healthy control men.

Gender and age are thus known to influence emotion processing ability in healthy adults separately and have recently been shown to influence emotion processing accuracy in MDD differentially. However, much less is known about how these characteristics together affect the neural circuitry supporting emotion processing in individuals with MDD. Developing a greater knowledge of these effects and interactions is crucial to understanding the mechanisms underlying emotion processing disruption in MDD. If there are global or interactive effects of these characteristics, it is possible that heterogeneity in the literature can be constrained and better understood. As such, this manuscript will provide a review of pertinent literature in the aforementioned areas, and propose a study examining the contribution of and interaction between gender and age to the neural circuitry supporting emotion processing in depressed individuals.

Emotion processing decrements in MDD

One common feature of major depressive disorder is interpersonal dysfunction (de Mello, Mari, Bacaltchuk, Verdeli, & Neugebauer, 2005). Individuals with MDD often withdraw from

social interactions with others, which is a distressing aspect of the disorder and is likely related to maintenance of symptoms. For example, social support and interactions may form a buffer, or even help ameliorate symptoms, yet withdrawal is the more frequent response observed. Facial expressions of emotion provide a unique and primary source of emotional and social information in interpersonal interactions (Adolphs, 2002; Williams & Gordon, 2007). More specifically, the ability to quickly and accurately interpret an emotion demonstrated in another's face is necessary in order to formulate an appropriate social response. As such, deficits in the ability to accurately and rapidly detect and respond to the emotional content in other's faces could greatly affect interpersonal functioning, lead to interpersonal difficulties, and subsequently to social withdrawal (Wright & Langenecker, 2008).

Prior work has demonstrated that difficulty in quickly and accurately identifying emotional expressions in faces is an emotional-cognitive deficit in individuals who suffer from MDD. Specifically, adults with MDD have been demonstrated to exhibit decreased accuracy and efficiency in their ability to recognize emotions in other's faces (Csukly et al., 2009; Persad & Polivy, 1993; Suslow et al., 2004; Langenecker et al., 2005; Langenecker, Caveney, et al., 2007). Although these deficits appear to be more severe in those with increased MDD severity (Gur et al., 1992), they have also been shown to be present even in remitted MDD (LeMoult, Joormann, Sherdell, Wright, & Gotlib, 2009). With regard to facial stimuli, deficits appear to be more pronounced with more subtle facial displays of emotion (Csukly et al., 2009, LeMoult et al. 2009), perhaps a reflection of increased difficulty. In contrast, MDD-related deficits in facial emotion processing (FEP) have not been reported with simpler facial recognition challenges (e.g., a simple two-stimuli forced choice paradigm with a given emotion (e.g., Archer, Hay, & Young, 1992)) classifying whether the face is emotional or neutral (e.g., Almeida, Versace,

Hassel, Kupfer, & Phillips, 2010). With regard to types of emotions, several studies have demonstrated a negative response bias for emotion classification (e.g., Gur et al., 1992; Kan, Mimura, Kamijima, & Kawamura, 2004; Yoon, Joormann, & Gotlib, 2009), such that individuals with MDD are more likely to ascribe a negative emotion to a given facial expression. As such, there is substantial evidence to indicate that adults with MDD have greater difficulty than healthy adults at quickly and accurately identifying emotions in faces. This decrement appears to be more pronounced with greater MDD severity and with more subtle displays of emotion, and when errors are made, those suffering from MDD may be most likely to erroneously perceive a negative emotion.

Decrements in emotion processing circuitry in MDD

One neurobiological hypothesis for the cause of this observed dysfunction in FEP in MDD is that deficits in FEP are related to dysregulated neural circuitry supporting processing of emotional stimuli. There is a strong body of research with evidence of disturbed emotion processing circuitry in MDD, which will be reviewed. To place these findings in context, however, facial emotion processing circuitry in healthy adults will be evaluated first.

Emotion processing circuitry in healthy adults. In healthy adults, two networks are thought to underlie emotional processing, according to Phillips and her colleagues (2003a). They proposed that the emotion processing network can be divided into a ventral and a dorsal system. The ventral system is composed of the amygdala, insula, ventral striatum, ventral anterior cingulate, and ventral prefrontal cortex, which together are involved in identifying the emotional significance of a stimulus, producing affective states, and regulating emotional responses. The dorsal system, comprised of the hippocampus, dorsal anterior cingulate, and dorsolateral

prefrontal cortex, is involved in executive functioning aspects of emotion processing, including selective attention, planning, and effortful regulation of emotional states.

With regard to processing emotions in faces, the ventral and dorsal processing systems have also been shown to be important. Specifically, the amygdala and orbitofrontal cortex (OFC) are well-demonstrated to play a crucial role in facial emotion processing (e.g., Adolphs, 2002; Price & Drevets, 2010). Damage to the amygdala results in impaired facial emotion classification, particularly for facial expressions of fear (Adolphs, Tranel, Damasio, & Damasio, 1994; Adolphs et al., 1999); this observation has led to the hypothesis that the amygdala is particularly involved in processing threat or danger. Alternative theories, however, have proposed that the amygdala is more generally activated during salient events (Phillips et al., 2003a). Functional neuroimaging studies have demonstrated differential involvement of the amygdala depending on the experimental task. For example, some studies (e.g., Critchley, et al., 2000; Hariri, Bookheimer, & Mazziotta, 2000) have demonstrated decreased involvement of the amygdala during tasks with greater cognitive demands (e.g., labeling an emotion vs. labeling gender), whereas other studies (e.g., Gur et al., 2002) have reported the opposite pattern.

Damage to the orbitofrontal cortex results in impaired recognition of facial emotion (Hornak, Rolls, & Wade, 1996). The OFC may be specifically involved in the cognitive aspect of labeling emotions. The high degree of interconnection between the OFC and amygdala suggest that they work together in a network, possibly in order to direct attention to emotionally salient stimuli and then to categorize emotional expressions (Adolphs, 2002).

In addition to emotion-specific circuitry, visual processing areas appear to be preferentially involved in the perceptual aspects of processing facial stimuli. Specifically, the inferior occipital lobe appears to be involved in early perceptual aspects of facial features

(Haxby, Hoffman, & Gobbini, 2000), and the fusiform gyrus, famous for its involvement in processing faces, appears to be specialized for processing static facial characteristics (and thus for encoding face identity; Adolphs, 2002; Haxby et al., 2000). In contrast, the superior temporal gyrus seems to be preferentially involved in encoding the changeable or dynamic aspects of faces (and thus for encoding movement, gaze direction, etc.; Adolphs, 2002, Haxby et al., 2000). The anterior temporal lobe may be involved in linking the facial information to autobiographical information about that individual (e.g., name, identity).

A recent meta-analysis of studies investigating brain areas involved in facial emotion processing (Fusar-Poli et al., 2009) is largely supportive of the aforementioned findings. These authors found that general face processing (i.e., viewing faces compared to baseline) was associated with activation in visual processing areas (i.e., fusiform gyrus, middle/inferior occipital gyrus, lingual gyrus), in addition to medial prefrontal cortex, temporoparietal areas (parietal, middle temporal, and insula), limbic regions (amygdala, parahippocampal gyrus, posterior cingulate gyrus), putamen, and cerebellum. With regard to specific emotions, viewing neutral expressions (compared to baseline) was associated with visual (fusiform, left lingual, insula), frontal (left medial, right middle, precentral gyrus), and limbic (left amygdala and cingulate) areas, right lentiform nucleus, and cerebellum. Compared with neutral faces, happy faces were associated with activation in bilateral amygdala, left fusiform, and right anterior cingulate gyrus; sad faces were associated with right amygdala and left lingual gyrus; angry faces with left insula and right inferior occipital; fear with bilateral amygdala, fusiform, and medial frontal; and disgust with bilateral insula, right thalamus, and left fusiform gyrus. As such, in healthy adults, processing an emotional expression in a face involves a distributed neural system, including a variety of visual processing areas and an emotion-specific network, with

different areas appearing to be preferentially involved in processing particular emotions. Taken together, these studies suggest that a distributed neural network is crucial for facial emotion processing, including visual perceptual networks, emotion-specific networks, and regulatory networks.

Facial emotion processing circuitry in MDD. Functional neuroimaging studies have demonstrated disruption in the neural circuitry supporting emotion processing in individuals with MDD. One model of general emotion processing disruption (Phillips, Drevets, Rauch, & Lane, 2003b) posits that dysfunction in emotion processing in MDD is the result of abnormal processing in the ventral and dorsal emotion processing circuitry. According to this model, increased activity in the ventral circuit (e.g., amygdala, insula, ventral striatum, ventral PFC), results in a restricted range of emotional responses, driven by a negative bias (i.e., tendency to perceive negative as compared to positive emotions). Concurrently, dysregulation of the dorsal system (e.g., DLPFC, dorsal anterior cingulate, hippocampus) reduces effective modulation of the ventral system, thus potentiating the phenomena. Causal factors underlying this disrupted processing may include differences in neural transmission, neurotransmitter/ neuroreceptor functions, in addition to disease-related factors altering cell health, including alterations in number of cells and synaptic connections and processes relating to cerebrovascular or thyroid dysfunction (Drevets, 2000).

A similar circuit has been demonstrated to be disrupted with regard to emotion processing in MDD specific to facial emotions. Disrupted activity of the amygdala is one of the most commonly studied aspects of FEP disruption in MDD. The majority of such studies have demonstrated amygdala hyperactivity (e.g., Dannlowski et al., 2008; Fu et al., 2004; Sheline et al., 2001) in response to FEP, but not universally so (e.g., Lawrence et al., 2004; Surguladze et

al., 2005). Other studies have suggested that the amygdala behaves in an emotion specific manner, with hyperactivity of the amygdala for sad faces and hypoactivity for happy faces (Suslow et al., 2010). Also, Sheline and colleagues (2001) reported amygdala hyperactivity for happy and sad, but not neutral faces. Interestingly, one study reported that in depressed adults, greater accuracy in classification of faces as emotional vs. neutral was associated with less activity in the left amygdala (Almeida et al., 2010), whereas another study reported greater amygdala activity associated with greater negative response bias (Dannlowski et al., 2007), suggesting that amygdala hyperactivity may contribute to poorer facial recognition accuracy.

Disrupted activity in various frontal regions in MDD has also been consistently reported in this literature. Middle and superior frontal hyperactivity (Briceno et al., in press; Frodl et al., 2009) and inferior frontal hyperactivity (Briceno et al., in press) have been reported. Lawrence et al. (2004) reported DLPFC hypoactivity for fearful, happy, and sad faces. Some studies have also shown altered activity in the precentral gyrus (Frodl et al., 2009; Briceno et al., in press) and anterior cingulate (Lee et al., 2008; Briceno et al., in press). The orbitofrontal cortex has also been shown to be hypoactive, particularly for sad faces (Lee et al., 2008; Lawrence et al., 2004). Interestingly, a recent study utilizing functional connectivity (de Almeida et al., 2009) found reduced connectivity between the left orbitomedial PFC and amygdala for happy faces (and trend level relationship for sad faces), suggesting that the reduced functional synchrony between these two areas may underlie dysfunction in each region.

Disrupted activity of the basal ganglia is another frequently reported finding in MDD. Both hypoactivity (Fu et al., 2007; Lawrence et al., 2004; Lee et al., 2008) and hyperactivity (Briceno et al., in press; Fu et al., 2004) have been reported. Surguladze et al. (2005) reported hypoactivation of the (right) putamen for happy faces, and hyperactivation of the (left) putamen

for sad faces, suggesting that the specific emotion of the facial expression may modulate the disrupted activity.

Finally, a number of other cortical and subcortical regions have been reported to be disrupted in MDD. Hyperactivity has been reported in cortical structures including fusiform (Surguladze et al., 2005), insula (Fu et al., 2004; Briceno et al., in press), parietal (Briceno et al., in press; Frodl et al., 2009; Fu et al., 2004), and temporal (Briceno et al., in press) regions, and subcortical regions including thalamus (Briceno et al, in review, Lawrence et al., 2004; Fu et al., 2004;), middle/posterior cingulate (Frodl et al., 2009; Briceno et al., in press), hippocampal formation (Fu et al., 2004; Lawrence et al., 2004), hypothalamus (Fu et al., 2004) and midbrain (Briceno et al., in press). However, a number of studies have reported hypoactivity of similar regions, including fusiform gyrus (Surguladze et al., 2005), parietal, occipital and cingulate gyri, and thalamus (Fu et al., 2007), hippocampal formation (Fu et al., 2007; Lawrence et al., 2004; Lee et al., 2008; Briceno et al., in press), and cerebellum (Frodl et al., 2009; Fu et al., 2007).

As such, although substantial variability exists in reported studies to date, most consistent findings include disruptions in limbic, frontal, and striatal circuitry in face emotion processing in MDD. The degree of variability in these findings is not surprising given the varied methodology used in these studies, such as imaging parameters, patient characteristics (e.g., heavily women vs. gender-balanced, inpatient vs. outpatient, medicated vs. unmedicated), paradigm specificity (e.g., specific or non-specific to different types of emotions), and analysis strategy (region of interest (ROI); whole brain). Most of the experimental tasks used in these studies include implicit processing of emotions, such as passive viewing of stimuli (e.g., Lee et al., 2008), presenting faces masked and thus outside of conscious awareness (e.g., Dannlowski et al., 2008; Dannlowski et al., 2007), and gender discrimination decisions (e.g., Canli et al., 2005;

Costafreda et al., 2009). Fewer studies have employed explicit emotion judgments, including general emotional classification decisions about facial expressions (e.g., emotional vs. neutral, e.g., Almeida et al., 2010), matching emotions presented in different faces (e.g., Frodl et al., 2009), and choosing a verbal label to describe a presented facial expression (e.g., Briceno et al., in press). The majority of studies have utilized either implicit or simplified emotion classification tasks, which often fail to demonstrate behavioral performance differences between groups. Although this line of research has provided invaluable information with regard to the automatic processes underlying face emotion processing, it precludes the investigation of the role that performance variables, or behavior, play in the neural responses to facial emotions, and has resulted in a disconnection between the well-established body of behavioral literature demonstrating facial expression recognition accuracy decrements and the neural circuitry underlying these decrements. As such, it remains unclear the role that behavioral dysfunction *per se* relates to the activation of emotion-specific circuitry in individuals with MDD.

Emotion processing and gender

Overall, studies investigating emotion processing circuitry in MDD have varied greatly with regard to the balance of men and women in their samples, and none have directly evaluated gender differences. This fact is surprising, given the consistent findings of gender differences in emotion processing in healthy adults. More specifically, women are more accurate and faster at detecting facial expressions of emotions than men (Thayer & Johnsen, 2000; Hampson, van Anders, & Mullin, 2006; Rotter & Rotter, 1988; Williams et al., 2009), a finding that is present from early childhood (for a meta-analysis see McClure, 2000). Some studies have suggested that the women-related advantage is particularly salient for negative as compared to positive emotions (e.g., Hampson et al., 2006, Williams et al., 2009), possibly a reflection of the fact that

negative emotions are typically more difficult to identify (e.g., Calder et al., 2003). Hypotheses for the processes underlying this women-specific advantage range from evolutionary (e.g., Hampson et al., 2006), to sociocultural (e.g., Rotter & Rotter, 1988), to neurobiological (e.g., Lee et al., 2002). Most pertinent to the present study, the neurobiological hypothesis suggests that women's advantage in FEP is related to differences in neural circuitry underlying emotion processing. Studies evaluating this hypothesis will be described, as follows.

A number of studies evaluating gender differences in facial emotion processing have reported that women exhibit greater activation in limbic (e.g., amygdala, Kempton et al., 2009; parahippocampal gyrus, Aleman & Swart, 2008) and frontal (Aleman & Swart, 2008) areas. However, increased activation in women in these areas has not been universally reported, as a few studies have reported greater frontal activation in men (Kempton et al., 2009; Lee et al., 2002) and one study (Derntl et al., 2009) reported no gender differences in amygdala activation. With regard to other brain areas, some studies have reported increased activation in women compared to men in visual processing areas (Lee et al., 2002; Kempton et al., 2009), insula (Aleman & Swart, 2008), parietal lobe, and thalamus (Lee et al., 2002). Women have also been shown to exhibit greater temporal activation than men (e.g., Kempton et al., 2009), although this finding may be dependent upon particular facial expressions (e.g., Lee et al., 2002, women exhibited greater temporal activation than men for happy faces, but men exhibited increased temporal activation for sad faces compared to women) or laterality (i.e., Aleman & Swart, 2008, women demonstrated increased activation compared to men for right temporal lobe, but women demonstrated decreased activation compared to men for left temporal lobe). Finally, one study (Lee et al., 2002) found increased right putamen/globus pallidus activation for sad faces in men, but increased left putamen/globus pallidus activation for sad faces in women.

With regard to laterality, two studies found more right-lateralized activation in men (Hall, Witelson, Szechtman, & Nahmias, 2004; Killgore & Yurgelun-Todd, 2001). Killgore and Yurgelun-Todd (2001) found that the pattern of laterality in the amygdala depended on the specific emotion displayed, such that men demonstrated more right lateralized activation in amygdala for happy faces, but more left lateralized activation for fearful faces. Findings by Lee et al. (2002) were somewhat consistent with these prior studies, in which both men and women's activation were more left lateralized for happy faces, but for sad faces, women demonstrated more left lateralized, and men demonstrated more right lateralized patterns of activation. The behavioral laterality literature (e.g., Harrison, Gorelczenko, & Cook, 1990) has demonstrated greater right laterality in men than women in facial emotional processing, as demonstrated by faster reaction times for faces presented to the left compared to the right visual field in men, but a lack of such a difference in women. As such, there is evidence to suggest that men tend to utilize more right hemisphere resources than women in processing facial emotions, although this pattern may depend on the specific emotion being displayed.

Taken together, these studies suggest that differences exist in the neural resources that men and women utilize in processing facial emotions, with women tending to utilize greater limbic and frontal resources, whereas men may recruit greater visual processing and other cortical structures. Furthermore, men may recruit more right-lateralized resources than do women. However, as in the MDD literature, variability in gender differences appears to be the rule rather than the exception, with differences in findings likely attributable to differences in specific emotions, scanning parameters, task design, and in experimental task demands.

Gender differences in emotion processing in MDD

Given the presence of gender differences in healthy adults for both FEP accuracy and the neural circuitry underlying it, in addition to the substantially increased risk of MDD in women compared to men (Weissman et al., 1996), it is conceivable that gender could be an important moderator of facial emotion processing dysfunction in MDD. However, extant studies evaluating facial emotion processing decrements in MDD have failed to evaluate the influence of gender, and a large proportion of these studies have used exclusively women (e.g., LeMoult et al., 2009; Persad & Polivy, 1993; Langenecker et al., 2005) or women-predominant samples (e.g., Archer et al., 1992; Gur et al., 1992). As in the behavioral literature, neuroimaging studies of facial emotion processing in MDD have typically ignored gender (see Table 1; Appendix A). As such, the applicability of the findings from these studies to both men and women with MDD is indeterminable.

Only one study (Wright et al., 2009) has evaluated gender differences in behavioral aspects of facial emotion perception in MDD in young adults (i.e., those under age 40). These authors found an interaction between MDD and gender, such that depressed women were less accurate at detecting emotions than both healthy control women and depressed men, whereas depressed men performed similarly to control men. More specifically, women with MDD were most likely to misclassify sad and fearful faces as compared to the other groups, and were more likely to misclassify these emotions as anger. Women with MDD also demonstrated greater negative emotion processing cost, quantified as the difference in response time between positive (i.e., happy) and negative emotional stimuli. As such, this preliminary evidence suggests that women with MDD may be uniquely vulnerable to facial emotion processing deficits. Furthermore, these data call into question the generalizability of prior findings with regard to

emotion processing deficits in MDD; specifically, it is possible that prior findings with regard to depression were largely driven by decrements specific to women with MDD.

The factors underlying this women-specific decrement in FEP in MDD are unclear. Wright et al. (2009) suggested that this phenomenon might be related to gender differences in pathogenic factors leading to MDD. More specifically, given the importance of face emotion processing in interpersonal functioning, and the differentially greater importance of interpersonal relationships for women (Cyranowski, Frank, Young, & Shear, 2000), it is possible the women with emotion processing deficits may have reduced effectiveness in interpersonal relationships, which would then serve as a risk factor for developing MDD. An alternative, and perhaps complementary, hypothesis is that this deficit may be the result of gender differences in how MDD affects emotion processing circuitry. As reviewed above, in healthy adults, women activate greater limbic and frontal structures than men. In depressed states, in which limbic and frontal hyperactivity is often observed, it is possible that this disruption differentially affects women, who already have higher "baseline" levels of activation in these areas, which in the context of MDD, may interfere with accuracy in facial emotion processing.

In spite of the compelling evidence outlined above, there have been no studies to date that have specifically addressed gender differences in emotional circuitry underlying facial emotion processing in depressed adults. However, a recent review of structural neuroimaging literature in adults with MDD (Lorenzetti, Allen, Fornito, & Yucel, 2009) identified gender differences in structural abnormalities in MDD. For example, women are more likely to demonstrate volumetric reduction in the amygdala compared to men. In addition, men, but not women, have demonstrated reduced medial prefrontal cortex volumes. Finally, contradictory gender differences in the subgenual anterior cingulate cortex (ACC) have been reported, with one study

showing women-specific reductions and another study showing men-specific reductions. The authors of this review acknowledged that, overall, the literature with regard to gender differences is sparse.

Taken together, although no studies have evaluated how gender affects disruption in the neural circuitry supporting FEP in MDD, there is compelling evidence that gender may play a crucial moderating role. First, women are more susceptible to developing MDD. Second, preliminary evidence has demonstrated a women-specific decrement in FEP accuracy decrements in MDD. Third, some structural differences appear to be present in men and women with MDD in regions pertinent to emotion processing. Finally, gender differences in behavioral performance and in neural circuitry supporting FEP are present in healthy adults. A study directly investigating gender differences in FEP in MDD will be important for determining whether general findings with MDD are generalizable to both men and women, and to contribute to a better understanding of the specificities of the pathogenesis and expression of MDD in men and women.

Emotion processing and aging

Behavioral literature indicates that elders are less accurate than younger adults at identifying emotional expressions in faces. This vulnerability appears to be most prominent for negative as compared to positive emotions (e.g., Calder et al., 2003), Sullivan & Ruffman, 2004; Moreno, Borod, Welkowitz, & Alpert, 1993; Williams et al., 2006), and some studies demonstrate improved performance among elder, relative to younger adults for positive emotions (e.g., Williams et al., 2006; Moreno, 1993). There are two main explanations that have been proposed for this age-related vulnerability. A sociocultural explanation suggests that elders have improved emotion regulation, which may result in reduced processing of negative affect. The

socioemotional selectivity theory (e.g., Charles & Carstensen, 2009) suggests that elders tend to prioritize their social world to reduce negative influences, resulting in improved overall emotional experience. In contrast, others (e.g., Labouvie-Vief & Medler, 2002) suggest that reduced negative affect in elders is accompanied by a reduction in affect complexity. Supporting the notion of reduced negative affect in aging, elder adults have been demonstrated to have reduced frequency of the experience and expression of negative emotions (e.g., reduced neuroticism, Williams et al., 2006), which in one study (Suzuki, Hoshino, Shigemasu, & Kawamura, 2007) was shown to be related to reductions in the ability to recognize sad faces.

Alternately, a neurobiological explanation suggests that reduced accuracy in facial expression recognition is the result of decreased efficiency in emotion processing networks in the brain, which may differentially affect negative as compared to positive emotion processing areas. Finally, preserved performance for positive and worsened performance for negative emotions could be an artifact of difficulty. Accuracy is typically worse for negative as compared to positive emotions, irrespective of age, gender, or disease status (e.g., Wright et al., 2009).

A few studies have examined the neural circuitry underlying facial emotion processing decrements in healthy elders. The most consistent finding in studies of facial emotion processing in healthy aging is that young adults tend to exhibit increased activity in limbic structures compared to elder adults, whereas elder adults tend to recruit increased cortical structures compared to younger adults. Specifically, the majority of these studies have reported increased amygdala activation in young compared to elder adults (Fischer et al., 2005; Gunning-Dixon et al., 2003; Iidaka et al., 2002; Tessitore et al., 2005; Williams et al., 2006), although some of these studies were specific to negative emotional stimuli (Fischer et al., 2005, Tessitore et al., 2005). Older adults, in contrast, recruit more frontal resources, including inferior and middle

frontal (Gunning-Dixon et al., 2003), medial (Williams et al., 2006; Tessitore et al., 2005) and ventral (Tessitore et al., 2005) prefrontal cortex. Less consistently, young adults have shown greater activity of the parahippocampal gyrus (Iidaka et al., 2002) and other various subcortical (caudate; Williams et al., 2006; midbrain, Iidaka et al., 2002), and other cortical (posterior fusiform, Tessitore et al., 2005; angular, lingual, Iidaka et al., 2002) areas, and elder adults have shown greater activation in the insula (Fisher et al., 2005).

Age and gender interactions in healthy adults. Gender has been largely ignored in studies of aging and emotion processing (e.g., Calder et al., 2003; Sullivan & Ruffman, 2004; Isaacowitz et al., 2007). However, one study (Williams et al., 2009) conducted a large-scale investigation of the effects of age and gender in FEP in individuals across ten decades (6 to 91 years). In this internet-based study, individuals viewed facial expressions of emotion and chose the label for the emotion expressed from six choices. They found that overall, women outperformed men and younger adults outperformed elder adults. They also found that an interaction between age, gender, and emotion, such that women's advantage at identifying fear and sadness was greatest for the elder adults; in addition, men demonstrated greater accuracy for anger in younger age groups. Interestingly, another study (Moreno et al., 1993) that investigated FEP and aging in a sample of women from young (20s and 30s), middle (40s and 50s) and elder (60s to 80s) groups found no main effects of age, suggesting that women may be less susceptible than men to the detrimental effects of age on FEP.

With regard to functional neuroimaging studies, although each of the studies previously reviewed on general aging effects included equal samples of men and women (see Table 1; Appendix A), only one of them evaluated the influence of gender (Tessitore et al., 2005). Although not the focus of the study, the authors evaluated gender differences in each of the

young (6 women, 6 men) and elder (7 women, 8 men) age groups and found no significant gender differences in activation. It is interesting to note that gender differences in activation were not reported in the young adults, a finding that is inconsistent with the numerous studies reviewed above (e.g., Aleman & Swart, 2008; Derntl et al., 2009), but likely due to low power with the limited sample size. Taken together, the literature on interactions between gender and age in FEP is too sparse from which to draw conclusions, as the scant behavioral literature (demonstrating age and gender interactions) appears to be inconsistent with the single imaging study (demonstrating no gender effects).

In general, however, gender does appear to be an important variable in understanding the neurobiology of aging. Studies have demonstrated both functional (e.g., Fujimoto et al., 2008; Kim, Kim, & Kim, 2009) and structural (e.g., Coffey et al., 1998) interactions between age and gender, such that men and women exhibit some differences in brain aging. For example, a structural study (Xu et al., 2000) found that men demonstrated greater atrophy than women in a variety of structures, including right frontal, right temporal, left basal ganglia, parietal lobe, and cerebellum.

Late-life depression: Definition and rationale for the subgroup of interest

Interest in depression in late-life has increased substantially in recent years, with studies investigating both phenomenological and neurobiological aspects of the disorder. This research has identified two distinct subgroups of individuals with depression with distinct neurobiological underpinnings, neuropsychological profiles, and symptom characteristics. Specifically, individuals with later age of onset (typically after 50 years) frequently demonstrate greater white matter pathology (e.g., white matter hyperintensities, reduced integrity of white matter tracts as demonstrated with diffusion tensor imaging), particularly frontal and subcortical (striatal)

circuitry (e.g., Figiel et al., 1991; Geerlings, den Heijer, Koudstaal, Hofman, & Breteler, 2008; Hickie et al., 1995; Lesser et al., 1996; Salloway et al., 1996). Individuals with late-onset depression also appear to have greater atrophy in frontal (Almeida, Burton, Ferrier, McKeith, & O'Brien, 2003; Andreescu et al., 2008) and striatal regions (e.g., Greenwald et al., 1997; Andreescu et al., 2008), whereas individuals with an earlier onset (EOD) appear to exhibit more reductions in medial temporal structures such as the hippocampus (HC; Bell-McGinty et al., 2002; Janssen et al., 2007), although this finding has not been entirely consistent (e.g., Andreescu et al., 2008; Greenwald et al., 1997; Ballmaier et al., 2008; Lloyd et al., 2004; Steffens et al., 2000). Third, individuals with late onset-depression have greater impairment in executive functions and processing speed (Herrmann, Goodwin, & Ebmeier, 2007; Lesser et al., 1996), which appears to be present even after remission of symptoms and has been linked to a poor or delayed response to antidepressants (Alexopoulos et al., 2005). Finally, symptom presentation by age of onset is distinct, such that individuals with early-onset depression are more likely to experience low spirits, feelings of worthlessness (Heun, Kockler, & Papassotiropoulos, 2000) and anxiety (Baldwin & Tomenson, 1995; Devanand et al., 2004) when compared to individuals with late onset, whereas individuals with late onset are more likely to exhibit somatic symptoms (Baldwin & Tomenson, 1995) and anhedonia (Lampe & Heeren, 2004; Lavretsky, Ballmaier, Pham, Toga, & Kumar, 2007). Finally, late-onset depression has been consistently shown to be related to a lower rate of familial depression (Devanand et al., 2004; Baldwin & Tomenson 1995; Hickie et al., 1995).

In light of this compelling evidence that early and late-onset depression reflect distinct neurobiological pathologies, and that late-onset depression appears to be a direct or secondary effect of cardiovascular/neurobiological processes rather than to neurodevelopmental

abnormalities in depression per se (e.g., Alexopoulos, 2006; Kendler, Fiske, Gardner, & Gatz, 2009), the current study chose to focus on early-onset depression. In other words, the intent of the current study is to investigate the *neurobiological burden* of depression accumulated over the lifetime, rather than the distinct syndrome of depression that first appears later in life. It should be noted that the investigation of the effects of *depression and aging* are intrinsically intertwined with the effects of *depression and chronicity,* or lifetime burden of depressive episodes. In order to separate out these two factors (i.e., the aging process from the chronicity/burden process) in the presentation of depression, it would be necessary to compare a large number of both early- and late-onset depressed individuals, in both active and remitted stages of depression; this type of investigation is outside the scope of the current study.

Emotion processing in depressed elders

There has been one behavioral study examining facial emotion processing in depressed elders (Wright & Langenecker, 2008). The focus of that study was on the interaction between MDD, age, and gender in facial emotion processing; as such, it will be reviewed in detail in a later section, below. With regard to main effects of MDD and age, the authors compared a group of young (35 years or younger) and middle/elder (36 years or older) adults with MDD and healthy controls. The authors found slowed reaction time for face emotion classification in the young MDD, but not the middle/elder aged MDD groups relative to age-matched control comparisons. With regard to accuracy, the MDD groups performed more poorly than the control group, and young adults outperformed the elder adults; however, there was no interaction between these characteristics. As such, these results suggest that reduced accuracy in facial emotion processing extends to middle/elder adults with MDD, but it may not be differentially affected by age.

The use of functional neuroimaging in late-life depression is still in its infancy, limiting our understanding of the neurobiological underpinnings of this effect. There have been very few studies in general utilizing functional neuroimaging in elder adults with depression. The few that have been conducted have either focused on LOD (e.g., Aizenstein et al., 2009; Ishizaki et al., 2008; Takami, Okamoto, Yamashita, Okada, & Yamawaki, 2007), have included a mixed sample of EOD and LOD (e.g., Hickie et al., 2007; Kumar et al., 1993; Lesser et al., 1995) or have not reported age of onset in their sample (e.g., de Asis et al., 2001; Nobler et al., 2000; Smith et al., 2009), rendering the applicability of their conclusions to adults with EOD and the neurodevelopmental underpinnings of the disorder unclear. Given the dearth of functional neuroimaging in geriatric depression in general, it is not surprising that the literature on neural circuitry underling emotion processing in depressed elders is nearly non-existent. Very few studies have investigated neural substrates of emotion processing in elder adults with depression, and each of the studies were either conducted with depressed adults with a late age of onset (Brassen et al., 2008; Wang et al., 2008) or age of onset was not reported (Alexopoulos et al., 2007). As such, the applicability of these prior studies to the current population of interest is limited at best; however, due to the paucity of the extant literature available on this topic, they will be reviewed.

The first study (Brassen et al., 2008) investigated the activity of the ventromedial prefrontal cortex (i.e., orbitofrontal cortex, rostral cingulate, and ventral medial frontal cortex) in a sample of first-episode, antidepressant-naïve, elderly women outpatients with mild to moderate depressive symptoms and compared them to healthy comparison participants. Participants completed an emotional evaluation task, in which they subjectively judged the emotional valence (i.e., positive, neutral, or negative) of adjectives presented to them. A region-of-interest analysis

was employed, focusing specifically on the ventromedial PFC regions. No differences between groups were present in valence ratings or reaction time. Comparing activation for negative to neutral words, neuroimaging data revealed reduced activation in the rostral ACC and medial OFC in the depressed group compared to controls. For positive compared to neutral words, depressed participants recruited greater medial OFC, whereas controls did not. For positive compared to negative words, depressed patients demonstrated greater activation for positive words in all regions in the ventromedial prefrontal cortex (vmPFC) compared to controls. Interestingly, patients were re-scanned approximately 7 months later following care as usual (i.e., antidepressants, behavior therapy, or no treatment); 12 of the 13 patients achieved remission. At this time, the patients demonstrated normalization of activation, such that no activation differences were present between depressed patients and controls. The authors concluded that dysfunction in the ventromedial PFC may be a state marker of depression in the elderly.

The second pertinent study (Wang et al., 2008) evaluated 12 adults with late-onset depression (7 women), all whom were over 60 years of age, and compared these patients with 15 remitted depressed participants and 20 controls. Eleven of the 12 patients and 12 of the 15 remitted participants were on antidepressant therapy. Participants completed an emotional oddball task, consisting of viewing attentional targets (circles) to which they were required to respond, in addition to sad and neutral distracters, and scrambled images. The authors concluded that depressed participants exhibited reduced activation in the executive system (i.e., right middle frontal, posterior cingulate, inferior parietal regions). Interestingly, although the middle frontal activation reduction was present only in the active depressed group, the reduced activation in the posterior cingulate and inferior parietal regions were also present in the remitted

group, suggesting a persistent disruption in executive systems, even following symptom remission.

In a third relevant study, Alexopoulos et al. (2007) recruited a group of individuals with geriatric depression, prior to and following treatment with antidepressants, to complete an emotional "go/no-go" task, in which they were presented with emotionally valenced words, and responded ("go") with a key press in response to a pleasant word, and did nothing ("no go") in response to an unpleasant word. The authors used event-related potentials to examine error-related negativity (ERN) and error positivity (EP), which are evoked potentials considered to be reflective of processing conflict, pre- and post- response, respectively, in the anterior cingulate. They found that those who did not respond to antidepressants had a larger ERN and smaller EP amplitude compared to treatment responders, suggesting that altered error-related processing in the anterior cingulate is important to understanding and anticipating treatment response in geriatric depression.

Taken together, these studies in elder individuals with MDD suggest altered brain activity in emotion processing tasks in individuals with geriatric depression. However, these three studies are heterogeneous in their focus, patient groups, experimental tasks, and brain areas evaluated, rendering any further conclusions tenuous at best. This review highlights the inadequacy of the current literature at elucidating how the neural circuitry underlying emotion processing is disrupted in early-onset geriatric depression.

Depression, aging, and gender

Given the paucity of data with regard to geriatric depression and emotion processing in general, as would be expected, there is very little literature with regard to whether gender may moderate this relationship. One study (Wright & Langenecker, 2008) investigated the effects of

depression, aging, and gender on facial emotion processing accuracy in a group of young (less than 36 years) and middle-aged/elder (greater than 35 years) depressed adults with a mixed age of onset, and age-matched healthy controls. The authors found that healthy control women outperformed MDD women in both the young and middle/elder age group. In men, however, healthy controls performed similarly to the MDD participants in the young age group, but in the middle/elder age group, MDD individuals performed more poorly than healthy controls. Post hoc analyses indicated that the middle/elder MDD men had greater errors than middle/elder healthy controls for fearful faces, but not for angry, happy, or sad faces. In contrast, in middle/elder women, the MDD deficit was not specific to any particular emotion. Finally, post hoc analyses revealed that although age of onset was a not a significant predictor of accuracy in the overall group, in middle-aged/elder men, those with later age of onset performed worse compared to middle-aged/elder men with early onset and all middle-aged/elder depressed women. As such, it appears that emotion processing deficits are present in both middle-aged/elder women *and* middle-aged/elder men with MDD. This deficit appears to be exaggerated for men with late-onset depression.

Although there are no studies investigating how gender and age together modulate emotion processing in depression, one study (Lavretsky et al., 2004) investigated sex differences in structural abnormalities in late life depression. The depressed adults were mixed between early and late age of onset (mean age of onset = 48.5, SD = 23.5 years) and were predominantly women (32 women, 9 men). The authors found that men in both MDD and control groups had greater medical burden, apathy, and psychomotor retardation than did women, and had smaller frontal volumes. After controlling for medical burden, there was a diagnosis by sex interaction, such that depressed men had the greatest amount of reduction in frontal volumes compared to the

other groups. As such, depressed men may to be more susceptible to detrimental effects of MDD on the brain. However, it is unclear whether this susceptibility may be largely driven by individuals with late-onset depression, and thus whether a set of intermediate medical/physiological factors may be responsible for both development of late-onset depression and greater vulnerability to structural decline.

Summary and statement of study purpose

In summary, much is yet unknown regarding the neural circuitry supporting facial emotion processing in depression. In young adults, the literature has largely ignored the role of gender in neuroimaging studies of facial emotion processing in depression, although recent behavioral evidence in depression, in addition to both behavioral and functional neuroimaging investigations of gender in healthy adults, have consistently demonstrated that gender differences exist in facial emotion processing. These gender differences may be particularly relevant to depression, given women's substantially greater susceptibility to suffering from it. Furthermore, the process of aging has been shown to affect both accuracy in facial emotion processing and the neural circuitry supporting it. Little is known about whether gender differences observed in the brain areas supporting facial emotion processing in young adults can be extended to elder adults. Finally, very little is known about how neurophysiological processes are affected as depression extends into late life, and no studies have investigated circuits supporting facial emotion processing in these individuals, nor how gender may modulate this potential disruption. Table 1 (Appendix A) contains a summary of studies evaluating the neural circuitry supporting facial emotion processing, separated by age, gender, and depression status. As is evident in this table, much is yet unknown about these relationships, with the preponderance of literature on younger healthy and depressed women. The present study sought to investigate each of these unanswered

questions. A large sample, comprised of 110 adults, with at least 10 adults in each age (young vs. elder), gender, and MDD (MDD vs. healthy control) subgroup, were recruited to complete a facial emotion perception task (Rapport et al., 2002; Langenecker et al., 2005, 2007) in the fMRI scanner. MDD status, gender, and age were evaluated to determine their relation to the brain regions and circuits supporting facial emotion processing.

Hypotheses and Aims

Aim 1. Examine the influence of age and gender on neural circuitry supporting emotion processing in healthy adults.

Much is yet unknown regarding the contributions of and interactions between age and gender in emotion processing circuitry in healthy adults. First, it was expected that prior findings on the neural substrates of face emotion processing would be replicated among the entire healthy sample (e.g., Fusar-Poli et al., 2009), such that 1a) The Face Emotion Processing Test (FEPT) would elicit activation of areas previously demonstrated to be involved in emotion processing, with particularly robust activation expected in frontal, limbic, and basal ganglia regions. Second, based upon prior findings (e.g., Aleman & Swart, 2008), it was expected that gender differences in the neural circuitry underlying face emotion processing in healthy young adults would be observed. Specifically, it was expected that 1b) women would demonstrate increased activation compared to men in frontal and limbic networks, and that men would demonstrate greater right lateralization of activation in response to the FEPT than would women. Third, with regard to the main effects of age, it was expected that 1c) young adults would exhibit more posterior (i.e., greater limbic, less cortical; Fischer et al., 2005; Gunning-Dixon et al., 2003; Tessitore et al., 2005) activation as compared to elder adults.

Interactions between age and gender in the neural substrates of emotion processing have not yet been investigated. The exploratory hypothesis was that age differences in emotion processing circuitry may be greater in women as compared to men, such that 1d) elder women would exhibit reduced limbic activity and greater frontal activation compared to younger women. Hypothesis (1e) predicted that reductions in limbic and increases in frontal activity would also occur in elder men compared to younger men; however, because these areas were relied upon less in young men than young women, the effect of age in men was expected to be less robust than that observed in women.

Aim 2: Investigate the influence of depression on neural circuitry supporting emotion processing.

Depression has been consistently demonstrated to alter neural circuitry supporting face emotion processing. It was expected that findings in this regard would be consistent with prior literature, such that 2) compared to healthy controls, depressed adults would demonstrate hyperactivity in limbic, basal ganglia, and frontal regions in response to the facial emotion processing task (Briceño et al., in press).

Aim 3: Examine the influence of age and gender in neural circuitry supporting emotion processing in depressed adults.

Based on the literature indicating age (e.g., Gunning-Dixon et al., 2003; Williams et al., 2006) and gender (e.g., Kempton et al., 2009) differences in emotion processing circuitry in healthy adults, in addition to the literature demonstrating age and gender interactions in emotion processing accuracy in depression (Wright & Langenecker, 2008), it was hypothesized that both gender and age would serve as moderators of the relationship between depression and neural circuitry supporting face emotion perception. Based upon evidence that depressed young women,

and not depressed young men, demonstrate decrements in face emotion processing accuracy (Wright et al., 2009), in addition to the disproportionate representation of women in functional neuroimaging studies of FEP in depression (Table 1; Appendix A) the exploratory hypothesis was that the effect of depression on the BOLD response to the FEPT in young adults would depend on gender. Specifically, it was hypothesized that: 3a) depressed women would demonstrate alterations in neural circuitry similar to that demonstrated in prior literature with regard to depression (i.e., disrupted activity of limbic, ventral striatal, and frontal regions), whereas 3b) Activation in depressed men would be more similar to that of control men and would be less congruent with general findings with respect to depression.

It was also expected that the effect of depression on neural circuitry supporting FEPT performance would be moderated by age. However, the existent literature was too limited to make specific predictions on how this disruption will occur, other than the exploratory hypothesis that 3c) Disruption in neural circuitry supporting emotion processing in depressed adults would be magnified in elder as compared to young adult groups. Finally, this study sought to 3d) explore the interactions between gender and age in neural circuitry supporting FEPT performance in elder depressed adults.

CHAPTER 2

METHOD

Participants

One-hundred-ten participants were recruited to participate in the present study, including 53 adults with Major Depressive Disorder (MDD) and 57 healthy control (HC) adults in younger and elder age groups. Table 2 (Appendix A) displays demographic characteristics of the sample. Participants were recruited through a variety of mechanisms, including through the University of Michigan Depression Center, geriatric psychiatry and primary care clinics, Claude D. Pepper Older Americans Independence Center human subjects database, and University of Michigan online clinical research database, in addition to advertisements within the community.

The *medical* exclusionary criteria were as follows: uncontrolled hypertension or diabetes, contraindications for MRI (e.g., metallic implants, pacemakers, weight greater than 250 pounds [due to scanner size], etc.), any neurological disorder (e.g., epilepsy), head injury with positive loss of consciousness of greater than 5 minutes, and those with major medical conditions that can affect the central nervous system, including heart, liver, lung, and similar diseases. Those with known or suspected past strokes were excluded. Participants were also excluded based upon presence or history of psychotic symptoms, bipolar disorder, schizophrenia, current substance abuse/dependence or history of substance dependence within 5 years of scan. As comorbidities are the rule rather than the exception in psychiatric disorders (e.g., Mineka, Watson, & Clark, 1998), in an effort to obtain an optimally representative sample of the population of interest, individuals with comorbid psychiatric diagnoses (with exceptions listed above) were included. Within the elder depressed group, individuals with an age of depression onset of 45 years or older were excluded from the study. Although this cutoff is more conservative than is

traditionally used in the literature (e.g., Heun et al., 2000), it minimized the likelihood of physiological features (i.e., cardiovascular, metabolic processes) contributing to the pathogenesis of the condition. Individuals were not excluded on the basis of taking psychotropic medications; however, those taking medications with known cognitive side effects (e.g., antipsychotics; benzodiazepines) were excluded.

Finally, those for whom English is not a first language and those with severe (and uncorrected) hearing or vision difficulties were excluded from the study. Right-handed dominant individuals were targeted for recruitment; however, when left-hand MDD patients were recruited, attempts were made to match healthy control participants to these MDD participants based upon age and gender. These exclusions are related to quality control in the data collection process and known lateralization literature for handedness and language.

Measures and Apparatus

Determination of MDD status and psychiatric screening. All participants in the MDD subgroups were diagnosed with MDD according to the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) criteria, by a licensed master's level (E.M.B.) or doctoral level (University of Michigan faculty and clinical neuropsychology postdoctoral fellows) psychologist. Forty-two were administered the Structured Clinical Interview for the DSM-IV (SCID-IP/NP; First, 1996) and 11 were administered a similar semi-structured clinical interview. Healthy control participants were screened for psychiatric illness with the non-patient SCID-I (n = 33) or a similar semi-structured interview (n = 24). Depression severity was measured with the Hamilton Rating Scale for Depression–Second Edition (HAM-D; Hamilton, 1960) and Beck Depression Inventory–II (Beck & Brown, 1996). Anxiety severity was measured with the analog clinician

and self-report scales (Hamilton, 1969; Beck, 1993) in a subset of participants recruited toward the end of data collection.

Emotion recognition paradigm. The Facial Emotion Perception Test (FEPT; Rapport, Friedman, Tzelepis, & Van Voorhis, 2002; Langenecker et al., 2005, 2007), completed in the fMRI scanner, has been used extensively as a measure of emotion processing and identification. Participants were presented with a series of photographs of faces (see Tottenham et al., 2009 for validation of facial stimuli) and were required to categorize each into one of four emotions (i.e., happy, sad, angry, fearful). After presentation of a fixation cross (500 ms), the stimulus (300 ms) and a mask (100 ms), participants were given a 2600 ms window to indicate their response with a button press. As a control task, blocks of animal photographs were presented in the same manner, in which they categorized the photographs into one of four groups (i.e., dogs, cats, primates, birds). The presentation of animal events (i.e., cross, stimulus, mask, response period) occurred for the same presentation and duration of time as the facial emotion blocks. Face and animal blocks were 24.5 seconds long and consisted of seven stimuli each. The task consisted of five, 3.5 minute runs and contained 56 animal presentations and 124 facial emotion presentations, including 30 neutral faces. Each trial in the imaging experiment was a novel presentation of an emotional stimulus per actor/actress, although the individual actor/actress did repeat. Primary behavioral dependent variables included accuracy and response time.

Functional Neuroimaging Parameters. Functional neuroimaging parameters were congruent with those used in other studies in our laboratory (e.g., Langenecker, Kennedy et al., 2007). Specifically, whole brain imaging was performed using a GE Signa 3T scanner (release VH3) between 2003 and 2012. The fMRI series consisted of 30 contiguous oblique-axial sections 4mm thick to cover the brain, acquired using a forward/reverse spiral sequence (Glover

& Thomason, 2004). The image matrix was 64 x 64 over a 24 cm field of view, resulting in a 3.75 x 3.75 x 4 mm voxel. The 30-slice volume was acquired serially at 1750 ms temporal resolution for a total of 590 time points. For the majority of participants, between 94 and 124 high-resolution Fast SPGR (Spoiled Gradient Recalled Acquisition in Steady State) Inversion Recovery (IR) axial anatomic images [TE (echo time) = 3.4 ms; TR (repetition time) = 10.5 ms, 27 degree flip angle, NEX (number of excitations) = 1, slice thickness = 1-1.5 mm, FOV (field of view) = 24 cm, matrix size = 256 x 256] were collected for coregistration. The initial 16 participants (8 HC women and 8 women with MDD) had 60 slice anatomical images with the same acquisition parameters except for slice thickness of 2-2.75 mm. They were recruited before the revised parameters with thinner slices were developed.

Procedure

Participants completed informed consent procedures per Institutional Review Board guidelines approved by the University of Michigan. Potential participants were contacted via phone and were screened briefly (e.g., demographic information; self-reported presence of depression, age of onset). If phone screening criteria were met, they were scheduled for in-person screening, in which they were administered a series of psychological and health screening measures. Participants were also administered a series of neuropsychological measures to be used in a separate study. FMRI testing occurred on a separate day; all participants obtained practice with the FEPT task prior to entry in the scanner, typically during the day of neuropsychological testing.

Functional neuroimaging analysis

Preprocessing stream. The preprocessing stream was initiated at the fMRI lab. Structural images were filtered to remove dielectric effects (Kristoff; cited in Strother, 2006), and the skull

was removed using the Brain Extraction Tool (Smith, 2002). Functional data were first filtered to remove white pixel artifact and converted to 3D images. Physiological artifacts were removed using the RETROICOR algorithm (Hu, Le, Parrish, & Erhard, 1995). Slice time correction was performed using "slicetimer" software from the FSL library (Bannister, 2002). Images were then realigned with the MCFLIRT software from the FSL library (Jenkinson, Bannister, Brady, & Smith, 2002).

The remainder of the preprocessing was conducted in SPM2. Functional images were first coregistered to the overlay image, then the overlay was coregistered to the SPGR image. Next, the SPRG image was warped to the Montreal Neurological Institute standard brain. Then, the functional images were normalized to the SPGR image. Finally, the normalized functional images were smoothed with a 5mm kernel. The Faces minus Animals contrast was computed for all Level 1 (i.e., individual) activation data, defined as activation for the Faces task minus activation for the Animals task. Level 1 activation data was analyzed with individual movement parameters entered as regressors.

Data screening- performance quality. For specific response sub-categories (e.g., happy) in which the frequency of responding was less than 50%, the score for that sub-category was prorated based upon performance in other categories. This low frequency of responding was most frequently present in elder adults and limited to one or two emotions, likely resulting from difficulty sustaining the minimal button press force required to indicate a response. To prorate the score, a within-sample *z* score for each of the emotion sub-categories was generated for each of the eight subgroups. The averaged *z* score for that individual for the remaining response sub-categories (e.g., fear, angry, sad) was used to prorate the individual category based upon the median score for all other individuals for that response category. Finally, the total accuracy score

was recalculated with the prorated sub-category score. The impact of this score on activation differences for all effects performed in the analysis is reported in the results section (i.e., *Influence of performance, clinical, and medical comorbidity variables in between-group differences).*

Data screening- Imaging quality. Data were thoroughly screened for sources of data corruption (e.g., signal loss due to scanner malfunction, movement artifact). First, individual masks were evaluated for signal loss. Typically, this resulted in subcortical signal loss, but more infrequently cortical signal loss was present due to uncorrected artifacts. Next, each individual (i.e., level 1) model was evaluated and assigned a subjective rating for quality of activation map, according to robustness of activation, in addition to localization of activation in task-relevant regions based upon a meta-analysis of facial emotion processing (Fusar-Poli et al., 2009; frontal, limbic, basal ganglia). Next, a leave-one-out analysis was conducted within each of the eight subgroups, screening for substantial change in activation maps (e.g., number of significant clusters) with removal of a single participant. For those individuals in which potential problems were identified through each of these screening mechanisms: 1) activation data were extracted in pertinent ROIs and were plotted across the time course to evaluate for presence of data corruption due to signal spiking, despiking, field inhomogeneities and signal drop-outs, or other non-task related irregularities in signal; 2) movement data over the time course were reviewed to evaluate data corruption due to movement.

Data cleaning, determination of final sample and data exclusion. When signal distortion was discovered for individual data points (e.g., spiking, despiking artifact, uncorrectable field inhomogeneities), these data points were removed and then interpolated from the nearest intact sequential images. The data screening process also revealed that one participant (an elder MDD

man) had extensive signal loss in all anatomical and functional images due to scanner dysfunction, and was thus excluded from the sample. One participant (elder HC woman) had an unusual head shape (oval and large); as such, the superior aspect of the cortex was not captured by the functional or structural MRI. Due to the exclusionary nature of the SPM mask at the Level 2 model, this participant was not included for group analyses. Two participants within the young HC women group had within-scanner movement of greater than 1.9 mm (corresponding to half of one voxel), and were thus excluded from group analyses. One participant (a young MDD woman) had significant signal distortion across several runs; extracted data revealed activation values that were greater than 3 SD above the group mean in greater than 50% of significant ROI's; she was subsequently excluded from the sample. A young HC man was excluded for excessive movement and signal distortion due to scanner malfunction, two young men with MDD and two young MDD women were excluded due to signal distortion due to scanner malfunction. Specifically, there were lateralized and/or anterior-posterior field inhomogeneities that distorted baseline and task signal to an extent that beta weights and statistical results were distorted. As such, all analyses were conducted with the remaining 100 participants. There were no substantial differences in demographic characteristics between this sample of 100 and the full sample.

Group analyses

A 2 (MDD status) by 2 (gender) by 2 (age group) factorial ANOVA was conducted, with thresholds meeting AlphaSim (Ward, 2000) criteria ($p < .005$, $k > 55$). This program takes into account the probability of height by extent thresholding, considering voxel size, spatial smoothing, and region of interest (in this case, whole brain). For evaluation of specific hypotheses, planned contrasts using *t* tests were conducted. All post hoc analyses were

conducted within SPSS using extracted data (mean signal change) from MarsBaR. This strategy allows for cluster-specific analyses, although use of cluster mean signal results in conservatively biased post hoc results.

To evaluate the potential influence of the control condition (i.e., Animals) upon group difference in the Faces minus Animals contrast, activation maps for the Animals Only contrast were superimposed upon the activation maps for the Faces minus Animals contrast for each result. If there was overlap between regions showing significant effects for Animals only and Faces minus Animals, those effects were noted in the respective table within the results section. Interpretation of these specific cluster effects was tempered as a result of the potential for obscurity with regard to animal categorization and facial emotion-driven (subtracted from animal-categorization driven) effects.

CHAPTER 3

RESULTS

Summary of ANOVA, overview section. To evaluate the effects of MDD status, gender, and age group on FEPT activation, an ANOVA was conducted within the full sample. MDD status, gender, and age group were independent variables, and activation within the faces minus animals contrast was the dependent variable. Statistical significance of the analyses was assessed using a combined height and extent threshold, as specified by AlphaSim (Ward, 2000) criteria ($p < .005$, $k = 55$). This analysis revealed main effects of MDD status (Table 3, Appendix A), gender (Table 4, Appendix A), and age group (Table 5, Appendix A). There were no regions significant for an interaction between MDD status and gender. There were two regions significant for an interaction between MDD status and age group (Table 6, Appendix A), and four regions significant for an interaction between gender and age group (Table 7, Appendix A). There were seven regions significant for an interaction between MDD status, gender, and age group (Table 8, Appendix A). Each of these findings will be discussed in more detail in the following sections, as they pertain to each of the study aims.

Aim 1. Examine the influence of age and gender on neural circuitry supporting emotion processing in healthy adults.

Analysis of Aim 1 was conducted within the HC group only, with a 2 (gender) by 2 (age group) ANOVA, with the Faces minus Animals contrast as the dependent variable. Statistical significance of the analyses was assessed using a combined height and extent threshold, as specified by AlphaSim (Ward, 2000) criteria ($p < .005$, $k = 55$). *T* test contrasts were conducted to evaluate specific hypotheses.

Overall task effect: Hypothesis 1a predicted that the FEPT would elicit activation in frontal, limbic, and basal ganglia regions in healthy adults. Within the ANOVA in the HC group, the main effect of task revealed support for this hypothesis. Table 9a (Appendix A) lists, and Figure 1 (Appendix B) illustrates, significant areas of task-related activation. Activation was significant in large bilateral clusters extending to inferior, middle, and superior frontal gyri and insula, right superior and middle temporal gyri, lingual gyrus, fusiform, and a large cluster extending to the putamen, thalamus, hippocampus and substantia nigra. To provide comparison of the present findings to prior studies of facial emotion perception conducted within young healthy control adults, the analysis was then restricted to the young HC group (i.e., a comparable one-sample *t* test). A similar, but larger, network was revealed, with similar activation extending to inferior, middle, and superior frontal gyri and insula, bilateral temporal lobes, precuneus, angular gyrus, cingulate, thalamus, right parahippocampal gyrus, and several cerebellar clusters. Results for this analysis are listed in Table 9b (Appendix A; Young HC participants).

Effects of gender: Hypothesis 1b predicted that women would exhibit increased frontal and limbic activation and greater left-lateralized activation as compared to men. Within the HC group, the main effect of gender revealed activation in one cluster, extending to the parahippocampal gyrus, fusiform, and culmen (Table 10, Appendix A; Figure 2a, Appendix B). Extracted data from this cluster revealed that this difference was driven by greater activation in

women as compared to men, t (51) = -3.71, p < .001, revealing partial support for this hypothesis. Brain regions significantly associated with the main effect of gender within the full sample (i.e., including the MDD group) are presented in Table 4 (Appendix A). Effect sizes for gender within these regions for the HC group are presented for comparison, and reveal similar magnitude of effect between groups.

Hypothesis 1b predicted that women would exhibit greater left-lateralized activation compared to men. To test the laterality hypothesis, a voxel-count analysis was conducted, comparing the number of significant voxels in the left and right hemispheres for the one-sample t tests (p < .005, k = 55) in women and men separately. The analysis revealed left-lateralized activation for both men and women. For women, the ratio of left to right significantly activated voxels was 2.12:1; in men, this ratio was 3.17:1. When the analysis was restricted to clusters in the frontal lobe, results were consistent (left to right ratios of 1.96 in women and 3.09 in men). As such, the gender-specific laterality hypothesis was not supported.

Effects of age group: *Hypothesis 1c predicted that young adults would exhibit more posterior (greater limbic, less frontal) activation compared to elder adults.* In the HC-only ANOVA, there were no clusters significantly associated with a main effect of age group. When the effect of age group was evaluated within the entire sample (i.e., including the MDD group; Table 5, Appendix A), effect sizes for age group within the HC group are presented for comparison. Effect sizes were similar between the full sample and the HC Only group, suggesting that the absence of an effect within the HC Only group was due to low power.

Interactions between gender and age group

Within the HC group, there were no regions of significant interaction between gender and age group. When the gender by age group interaction was evaluated within the entire sample

(i.e., including the MDD group; Table 7, Appendix A), several regions were associated with a gender by age interaction. Within these regions, effect sizes for the HC Only group are presented for comparison. Effect sizes were smaller in the HC group compared to the full sample, suggesting that the interactions in the full sample were driven by inclusion of the MDD group.

Effects of age group within women: *Hypothesis 1d predicted that elder women would exhibit reduced limbic and greater frontal activation as compared to young women*. Planned *t* contrasts (with a more lenient threshold of $p < .01$, $k = 55$ due to the small sample size, hypothesis-driven analysis and targeted regions) revealed greater activation in young compared to elder women in the subgenual cingulate/caudate region, bilateral parahippocampal gyrus and right amygdala. Elder women had greater activation than young women in medial frontal gyrus and cingulate. As such, Hypothesis 1d was partially supported. These results are reported in Table 11a and 11b (Appendix A), and illustrated in Figure 2, panel b (Appendix B).

Effects of age group within men: *Hypothesis 1e predicted that the effect of age group in men would be less robust than the effect of age group in women.* Planned *t* contrasts (with a more lenient threshold of $p < .01$, $k = 55$ due to the small sample size, hypothesis driven analysis and targeted regions) revealed greater activation in young as compared to elder men in the inferior frontal gyrus. Elder men exhibited greater activation than young men in large, bilateral parahippocampal clusters. These results are reported in Table 11c and 11d (Appendix A), and illustrated in Figure 2, panel c (Appendix B).

The robustness of the effects (effect sizes) was then specifically tested in the regions defined by age differences in women (Table 11a and 11b; Appendix A) and age differences in men (Table 11c and 11d; Appendix A). To do so, activation was extracted for these clusters and *d* scores were compared. In order for the hypothesis to be supported, there would need to be a

diminished *d* score difference in men compared to women in all clusters. Or, some clusters could exhibit diminished *d* score differences in men compared to women, and no clusters with an opposite effect. Analysis of *d* scores revealed that this hypothesis was not supported. Within all clusters defined by age differences in men, the effect of age upon activation within women was less robust than the effect of age within men.

Aim 2: Effects of MDD on neural circuitry supporting emotion processing in MDD

Main effect of MDD status. *Hypothesis 2 predicted that compared to the HC group, adults with MDD would demonstrate hyperactivity in limbic, basal ganglia, and frontal regions in response to the FEPT.* To evaluate Aim 2, the main effect of MDD status was evaluated in the 2 by 2 by 2 ANOVA for the total sample. The analysis revealed one cluster within the precuneus that was significantly associated with a main effect of MDD (MDD < HC, Table 3, Appendix A; Figure 3, Appendix B). Within the young adults only, *t* tests ($p < .005$, $k = 55$) revealed no areas in which activation differed between the control and MDD groups. As such, there is limited support for this hypothesis.

Aim 3: Effects of age and gender in neural circuitry supporting emotion processing in MDD.

To test the effects of MDD status, gender, and age group upon FEPT activation, an ANOVA was conducted within the full sample, with MDD status, gender, and age group as independent variables, and activation for the Faces minus Animals contrast as the dependent variable.

Interactions between MDD status and gender on FEPT activation. *Hypothesis 3a predicted that women with MDD would demonstrate alterations in neural circuitry similar to that demonstrated in prior literature with regard to depression* (i.e., disrupted activity of limbic, ventral striatal, and frontal regions). *Hypothesis 3b predicted that activation in men with MDD*

would be more similar to that of HC men and would be less congruent with general findings with respect to depression. There were no regions significant for an overall interaction between MDD status and gender, providing no direct support for this hypothesis.

Interactions between MDD status and age group on FEPT activation. The ANOVA revealed two clusters significant for an interaction between MDD status and age group, located in the precentral gyrus and dentate of the cerebellum. These clusters are listed in Table 6 (Appendix A) and illustrated in Figure 4 (Appendix B). To elucidate activation patterns across groups in these regions, data from the Faces minus Animals contrast were extracted using MarsBaR and post hoc analyses were completed in SPSS. For the precentral gyrus cluster, pairwise comparisons revealed a nonsignificant effect of MDD status in the young group (p = .22); in the elder group, the MDD group exhibited significantly less activation than the HC group (p < .001; illustrated in Figure 4, panel b, Appendix B). For the dentate cluster, pairwise comparisons revealed greater activation for the MDD group as compared to the HC group in the young group (p = .029), and less activation in the MDD as compared to the HC group within the elder group (p = .001; illustrated in Figure 4, panel d; Appendix B).

Interaction between MDD status, gender, and age group on FEPT activation. The 2*2*2 ANOVA revealed a number of regions significant for the three-way interaction, including clusters in the inferior, middle, and superior frontal gyri, cingulate, and putamen (Table 8; displayed in Figure 5; Appendix B). To elucidate activation patterns across groups in these regions, data from the Faces minus Animals contrast were extracted using MarsBaR and were further analyzed in SPSS.

Next, to decompose three-way interactions, two-way interactions were tested for each of the seven clusters within each age group, MDD status, and gender group separately (e.g., MDD

status and age group, separated by gender). Table 12 (Appendix A) reports the statistics for these analyses. Significant two-way interactions were then further explicated using post hoc pairwise comparisons ($p < .05$) as appropriate.

Interaction between MDD status and age group, separated by gender:

Within women, the interaction between MDD status and age group was significant for all seven clusters in the post hoc analysis. Pairwise comparisons revealed that in the young group, activation for the MDD group was greater than the HC group in four of the seven clusters, with the direction the same (MDD > HC) in the remaining three clusters. In the elder group, the MDD group exhibited less activation than the HC group in three of the seven clusters, with the direction the same (MDD < HC) for the remaining four clusters.

Within men, the interaction between MDD status and age group in the post hoc ANOVAS were significant for all seven clusters. Pairwise comparisons revealed that within young men, there was less activation in the MDD as compared to the HC group in four of the seven clusters, with the same direction (MDD < HC) for the remaining three clusters. Among the elder men, the MDD group exhibited greater activation than the HC group in three of the seven clusters; the direction was the same (MDD > HC) in the remaining four clusters.

Interaction between gender and age, separated by MDD status:

Within the MDD group, the interaction between gender and age group was significant for all seven clusters. In the young group, women had greater activation than men in all seven clusters. In the elder group, men had greater activation than women in six of the seven clusters, with the remaining cluster demonstrating the same direction.

Within the HC group, the interaction between gender and age group was not significant for any of the clusters.

Interaction between MDD status and gender, separated by age:

In the young adults, the interaction between MDD status and age group was significant for all seven clusters. Within young women, activation in the MDD group was greater than the HC group for four of the seven clusters, with the direction the same (MDD > HC) in the remaining three clusters. Within young men, the MDD group had less activation than the HC group in four of the seven clusters, with the same direction (MDD < HC) in the remaining clusters.

In the elder adults, activation was less in MDD women as compared to HC women in five of the seven clusters, with the direction equivalent (MDD < HC) in the remaining two clusters. Within men, activation was greater in MDD group as compared to the HC group in four of the seven clusters, with the pattern equivalent (MDD > HC) in the remainder of the three clusters.

The preceding evaluation of activation differences across groups revealed consistent patterns between groups across these clusters. As such, for the purposes of illustrating these patterns of activation differences between groups, activation values for each of the seven clusters were averaged into one value. These values are displayed in Figure 6 (Appendix B) for each of the eight subgroups, with two-way interactions marked. Figure 7 (Appendix B) displays these values with regard to each of the significant two-way interactions.

Entire Sample, Evaluation of Gender and Age Group

Main effect of gender. Within the full sample, there were two clusters significant for a main effect of gender (reported in Table 4, Appendix A and displayed in Figure 8, Appendix B). These clusters included the fusiform gyrus and middle temporal gyrus. Evaluation of extracted data revealed activation was greater in women than men in both clusters, a pattern that was consistent when the analysis was restricted to the HC group only. Comparison of activation

effect sizes between the full sample and the HC group only revealed similar, large effects between men and women in both clusters. Finally, to rule out underlying interactions between gender, age group, and MDD status for these clusters, two post hoc ANOVAs were conducted with gender, age group, and MDD status as independent variables, and activation for each cluster, separately, as dependent variables. These results revealed no significant interactions in either cluster (reported in Table 13a, Appendix A).

Main effect of age group. Within the full sample, there were four clusters significant for a main effect of age group (reported in Table 5, Appendix A; and displayed in Figure 9, Appendix B). These clusters included the right inferior frontal gyrus, cuneus and lingual gyrus, and pyramis of cerebellum. Post hoc evaluation of extracted data revealed that all four clusters exhibited greater activation in the young compared to the elder group, a pattern that was consistent when the analysis was restricted to the HC group only. Comparison of activation effect sizes between the full sample and the HC only group revealed similar, large effect sizes for the cuneus/lingual and pyramis cluster, and smaller effect sizes in the HC compared to the full sample in the IFG and lingual clusters (of large size in the full sample; of medium size in the HC group only). Finally, to rule out underlying interactions between gender, age group, and MDD status for these clusters, four post hoc univariate ANOVAs were conducted with gender, age group, and MDD status as independent variables, and activation for each cluster, separately, as dependent variables. These results revealed no significant interactions in any cluster (reported in Table 13b, Appendix A).

Interaction between gender and age group. There were four clusters significant for an interaction between gender and age group in the full sample (reported in Table 7, Appendix A and displayed in Figures 10 and 11; Appendix B). These clusters included the middle frontal

gyrus, precentral gyrus, claustrum, and pulvinar of thalamus. Within the full sample, post hoc pairwise comparisons revealed consistent patterns with regard to these interactions, with young women exhibiting greater activation than young men (significant for three of the four clusters and $p = .074$ for the fourth cluster), and elder women exhibiting less activation than elder men (significant for three of the four clusters and $p = .091$ for the fourth). Comparison of effect sizes between the full sample and the HC group only revealed consistently smaller effect sizes in the HC group only: in the middle frontal gyrus, a medium effect in the full sample and small effect in the HC-only sample; in the precentral gyrus and pulvinar, a large effect for the full sample medium effect for the HC-only sample; and for the claustrum/insula a medium effect in the full sample and a small effect for the HC-only sample. This pattern suggests that these interactions are driven by inclusion of the MDD group.

To evaluate the possible hypothesis that gender by age group interactions were driven by inclusion of the MDD group, activation for each cluster was tested for three-way interactions (i.e., with a series of MDD status by gender by age group post hoc ANOVAs). These results, summarized in Table 14 (Appendix A), revealed that activation in the middle frontal gyrus was significant for a MDD status by gender by age group interaction. To deconstruct this interaction, each of the two-way interactions was tested, holding the level of one variable constant (reported in Table 15, Appendix A). These results revealed that the three-way interaction was driven by 2 two-way interactions, as displayed in Figure 11 (Appendix B). Within the young group, the interaction between gender and MDD status was significant, such that women with MDD had greater activation than HC women, whereas the difference between men with MDD and HC men was not significant. In addition, the gender by age group interaction was significant in the MDD group. This interaction resulted from greater activation in women with MDD than men with

MDD in the young group, and greater activation in men with MDD than women with MDD in the old group.

Influence of performance, clinical, and medical comorbidity variables in between-group differences.

A series of analyses was conducted with extracted data to rule out non-target variables as responsible for the interactions between age, gender, and MDD status on FEPT activation.

FEPT performance. To investigate the potential influence of FEPT performance in between-group activation differences, a series of analyses was conducted. Table 2 (Appendix A) demonstrates differences in FEPT accuracy across groups, and unequal variance in accuracy across groups. As such, FEPT performance would not be suitable to use as a covariate in an analysis of covariance (ANCOVA). Instead, within each analysis of interest, the correlation between FEPT accuracy and activation was computed within the smallest relevant cell. Three of the 93 correlations were significant at $p < .05$, which is fewer than that which would be expected by chance (4.65 of 93 correlations would be expected to be significant by chance at a threshold of $p < .05$). As such, these relationships may be spurious. Significant correlations included the claustrum/insula and pulvinar clusters from the gender by age group interaction within elder women ($r = -.43$, $p = .045$; $r = .5$, $p = .020$, respectively) and the IFG/putamen cluster from the MDD by gender by age group interaction within elder depressed men ($r = 0.74$, $p = .009$).

Medical comorbidities. As displayed in Table 1 (Appendix A) and as expected based upon prior literature (e.g., Taylor et al., 2004), the subgroups differed with regard to presence of certain medical conditions. To evaluate the potential influence of these comorbid conditions upon between-group activation differences, effect sizes were computed first within the entire sample, then within the entire sample minus those with a specific medical condition (i.e.,

hypertension, heart condition, diabetes, sleep apnea). Overall, effect sizes were similar between the full sample and the full sample with these individuals removed. All effect sizes remained from medium to large, providing evidence that these medical conditions were not responsible for the effects observed.

Medication status. For each main effect and interaction identified in the preceding analyses, analyses were conducted within the MDD groups to evaluate whether results were explained by medication status. *T* tests were computed for each main effect and interaction to compare individuals with MDD who were and were not taking psychotropic medication. For the clusters significant in the three-way interaction, due to the small sample sizes within each cell, scatterplots were created to evaluate for potential effects. No differences were present in mean activation values between medicated and unmedicated MDD participants. Scatterplots of clusters significant in the three-way interactions, displayed in Figure 12 (Appendix B), did not reveal evidence for medication status as responsible for group effects.

CHAPTER 4

DISCUSSION

The present study found that both gender and age, independently and in combination, are pertinent to disrupted emotion processing circuitry in Major Depressive Disorder (MDD). Young women with MDD demonstrated hyperactive emotion processing circuitry, particularly within the inferior frontal gyrus, compared to healthy control (HC) young women. In contrast, young men with MDD demonstrated hypoactivation compared to young HC men in a number of task-relevant regions. The opposite pattern of results was present in the elder group, such that elder women with MDD exhibited hypoactivation compared to HC elder women; elder men with MDD exhibited hyperactivation when compared to elder HC men. When these subgroups were considered together, effects of depression appeared negligible, as they were obscured by the gender- and age-specific processes underlying emotion processing in MDD. Also of note, these findings cannot be explained by similar cognitive challenges that do not involve emotion, medical conditions, performance differences between groups, or medication status.

Gender differences in young adults with MDD

Within young adults, gender was an important moderator of emotion processing abnormalities in MDD. As expected, young women with MDD exhibited hyperactivity in a number of frontal regions, in addition to basal ganglia and limbic areas, compared to young HC women. Hyperactivity in emotion processing circuitry has been reported in several prior studies of facial emotion processing (FEP; Fu et al., 2004; Surguladze et al., 2005; Sheline et al., 2001), and it has been interpreted as a phenomenon relevant to MDD *in general*. The present study demonstrated that hyperactivity in emotion processing circuitry in young adults was present *only* in women with MDD. Young men with MDD, in contrast, exhibited *hypoactivation* compared to

young healthy control men in the same regions in which young women exhibited hyperactivation compared to healthy control women.

This finding of opposite gender effects in young adults with MDD is noteworthy, because prior studies combining men and women with MDD have obscured gender-specific mechanisms operating in MDD. Some hypotheses for mechanisms underlying hyperactive emotion processing circuitry include heightened sensitivity to affective material, increased difficulty regulating one's own emotional response to affective stimuli, and increased difficulty with task performance resulting in increased recruitment of resources to support performance. Hypoactivation in these same regions in men with MDD has not been previously reported. Hypoactivation has been infrequently reported in prior studies of emotion processing in MDD (e.g., Lee et al., 2008), and has been hypothesized to reflect dysregulated functional connectivity or reflective of underlying structural and functional connectivity. The present findings suggest a few additional possible explanations for this differential pattern of activation between men and women.

Differential recruitment by gender in young adults with MDD. It is possible that the hypoactivation observed in men with MDD reflects decreased network recruitment and engagement. In the present study, young men with MDD were less accurate in facial emotion processing as compared to young healthy men and young women. This finding is in contrast to a prior study (Wright et al., 2009) demonstrating a women-specific MDD deficit in facial emotion processing. Possible explanations for this discrepancy include differences in sampling and patient characteristics (e.g., fewer men with MDD in the present sample were taking psychotropic medications as compared to the men with MDD in the prior study).

Similar to hypotheses in literature with regard to healthy aging (e.g., Reuter-Lorenz & Cappell, 2008; Rypma & D'Esposito, 1999), in which task performance often is lower in old compared to young adults, the utilization of neural resources to support task performance may depend on the relationship between individual task demands and neural resource capacity. The intensity of these task demands differs between groups. In other words, as task difficulty increases, recruitment of neural resources may also increase, *until it reaches its maximum capacity*. When this maximum capacity is met and additional resources can no longer be dedicated to support performance, activation plateaus or even drops to reduced levels. Applied to the current findings, young men with MDD may have exceeded their resource capacity to support a highly demanding task, as their performance was most poor compared to the other groups of young adults. In contrast, young women with MDD may have been able to recruit the needed additional neural resources to support performance, yet not have reached maximum capacity. Future studies could evaluate this hypothesis using a facial emotion processing task that includes different levels of task difficulty.

Cognitive style in MDD. An alternative hypothesis for the present findings pertains to cognitive style in MDD. A large body of research has reported that women are more likely than men to ruminate, or engage in prolonged, negative thinking about their thoughts and emotions (Nolen-Hoeksema, Morrow, & Fredrickson, 1993; Tompkins, Hockett, Abraibesh, & Witt, 2011), as a strategy for coping with negative experience. Rumination has been demonstrated to be a risk factor for depression (Nolen-Hoeksema et al., 1993), and has been hypothesized to be one mechanism associated with the greater prevalence of depression in women compared to men (Nolen-Hoeksema, 2001). Thomas et al. (2011) found that within remitted adults with MDD, rumination was positively related to neural responses to negative facial emotions, and negatively

related to positive emotions. As such, young women with MDD may have more difficulty than men with MDD in their ability to disengage from negative affective stimuli, resulting in hyperactivation of emotion processing circuitry. Although the current study did not specifically investigate activation to negative emotions, the majority of facial emotions presented were negative. Thus, activation differences were likely driven more by processing of negative, as opposed to positive facial expressions.

In contrast to women's tendency to engage in prolonged thinking about their own thoughts and emotions, men may pay less attention to their emotions (e.g., Thayer et al., 2003) and are more likely to distract themselves (e.g., Hampel & Petermann, 2006) than women. Some evidence (e.g., Levant et al., 2009) suggests a greater rate of alexithymia, or difficulty identifying and expressing one's emotions, in men compared to women. Alexithymia has been shown to be related to depressive symptoms (Honkalampi, Saarinen, Hintikka, Virtanen, & Viinamaki, 1999). In addition, evidence (Berthoz, et al., 2002; Lee, et al., 2011) suggests that alexithymia is associated with reduced activity of neural regions supporting emotion processing tasks. Furthermore, some evidence suggests a link between disengagement coping (e.g., withdrawal) and depressive symptoms (Tompkins et al., 2011). As such, it is feasible that different cognitive styles associated with MDD in men (difficulty *maintaining engagement with* processing of affective material) and women (difficulty *disengaging from* processing of affective material) could result in discrepant patterns of activation supporting facial emotion processing. Future studies, incorporating measurement of rumination and alexithymia and selecting individuals with MDD exhibiting high and low on these characteristics, could further evaluate this hypothesis.

Gender differences in elder adults with MDD

The present study is the first to investigate the neural circuitry underling emotion processing in elder adults with lifelong, recurrent MDD. In elder adults with MDD, there were striking differences between women and men in the manner in which affective material was processed. Elder women with MDD exhibited reduced activation compared to elder healthy control women in a number of regions critical to facial emotion processing, whereas elder men with MDD exhibited greater activation in these same regions compared to elder healthy control men. These comparisons represent opposite effects to those that were observed in young adults with MDD.

The opposite gender-specific effects in elder compared to younger adults with MDD is surprising. The age threshold at which these effects may reverse, and the temporal pattern by which this reversal occurs, remains to be investigated. Given the small group sizes, especially with the known heterogeneity in late-life depression, this finding of different patterns of emotion processing in old and young men and women must be replicated. Is unclear whether this pattern reflects a gradual change throughout the aging process, or whether these effects begin to reverse at a particular age threshold. However, as this study was a cross-sectional design rather than longitudinal, the possibility of some cohort effect driving these differences cannot be ruled out. Longitudinal investigation of these processes, including adults with MDD throughout the age spectrum, would be particularly helpful to this regard. The mechanisms underlying these differences are unclear, as this area of inquiry in MDD has been vastly understudied. Neurobiological mechanisms that have been presented in the literature on healthy aging and geriatric depression may be relevant to the present results.

Recruitment hypothesis of differential gender effects in elders with depression. The recruitment hypothesis is a widely postulated explanation for differences in functional activation

for a number of cognitive tasks in healthy aging, in order to explain interactions between task performance and neural activation differences with aging (Rypma & Desposito, 1999; Reuter-Lorenz et al., 2008). In the present study, elder women with MDD demonstrated a tendency for poorer accuracy as compared to elder men with MDD. This pattern is opposite that observed in young adults with MDD (i.e., in which young men with MDD performed worse than young women with MDD). As such, it is feasible that the recruitment model proposed for young adults with MDD also applies (in a converse manner) to elder adults with MDD. In this model, elder men with MDD are able to recruit the neural resources necessary to support performance (i.e., they have not reached their resource capacity). In contrast, elder women with MDD may have exceeded their capacity for adequate recruitment, resulting in reduced activation. Intriguingly, and potentially at odds with this hypothesis, limited evidence on gender differences in late life depression suggests that men may be more vulnerable to the effects of MDD than are women. One study (Dal Forno, et al., 2005) reported that depressive symptoms increased the risk for onset of Alzheimer's disease in men, but not in women. In another study, depression was associated with a greater mortality in men, but not in women (Schoevers, et al., 2000). Lavretsky and colleagues (Lavretsky, Lesser, Wohl, & Miller, 1998) reported that elder men with MDD were more likely than women with MDD to exhibit neurovegetative signs and suicidal ideation, and more men than women with MDD exhibited large amounts of white matter pathology. However, these studies each incorporated those with late onset depression, which is associated with distinct neuropathology (Alexopoulus et al., 2001) and thus different potential gender-specific vulnerabilities. In elder adults with chronic MDD, the relative rates of neural decline are less well elucidated, and differential gender differences in these declines are feasible.

Gonadal hormones and brain function in elders with MDD. It is well established that depression is associated with dysregulation of a number of neurochemical systems, including those implicated in regulation of mood (e.g., serotonin) and the stress response (e.g., hypothalamic-pituitary-adrenal (HPA) axis). There exists a complex interplay between these systems (e.g., Armbruster, et al., 2011; Goel & Bale, 2010). Furthermore, it appears that sex steroids exert an important influence on HPA axis regulation (Viau, 2002) and mood-pertinent neurotransmitter regulation (Smith & Zubieta, 2001). This interplay in turn affects brain function and behavior (Steiner, Dunn, & Born, 2003). In elders with a recurrent lifetime history of MDD, these systems likely have been chronically dysregulated (e.g., Fries, Hesse, Hellhammer, & Hellhammer, 2005). Furthermore, sex steroid levels are known to decline with the aging process (Steiner et al., 2003; Seidman & Walsh, 1999), and lower levels of sex steroids appear to be associated with depression in elder adults (Steiner et al, 2003; Seidman & Walsh, 1999). The interaction between chronic dysregulation of the HPA axis and mood-pertinent neurotransmitter systems, combined with potential exaggerated decline of gonadal hormones in late life depression, may result in sex- disparate effects upon brain function in elders with MDD.

Estrogen, aging, mood, and brain function.

Estrogen has been implicated in mood and depression in elder women. Estrogen administration has been shown to be associated with improved mood in healthy elder women (Sherwin, 1991) and to augment antidepressant treatment response in some postmenopausal women (Rasgon, et al., 2007). Some evidence suggests that estrogen therapy in depressed postmenopausal women may be associated with improved treatment response (Steiner et al., 2003). Furthermore, it appears that estrogen levels are pertinent to the aging process in women: several studies have revealed beneficial CNS effects of estrogen replacement therapy (Smith &

Zubieta, 2001). Estrogen administration has been shown to be associated with increased functional connectivity between limbic and frontal regions (Peper, van den Heuvel, Mandl, Pol, & van Honk, 2011).

Estrogen levels have been shown to be pertinent to brain circuitry relevant to affective processing. For example, in young women with MDD, brain circuitry implicated in the stress response has been related to dysregulation of estrogen (Holsen, et al., 2011). Two studies (Love, Smith, Persad, Tkaczyk, & Zubieta, 2010; Shafir, et al., 2012) investigated exogenous administration of estrogen in healthy postmenopausal women and found differences between those treated and untreated in brain activation in response to an affective paradigm. Shafir et al. (2012) reported that postmenopausal women on long-term estrogen treatment had reduced activation compared to untreated women in the medial prefrontal cortex and left anterior cingulate gyrus during processing of positive affective material, and greater activation in the right entorhinal cortex during processing of negative affective material. Love et al. (2010) reported that during processing of negative affective material, short-term estrogen administration (compared to placebo) was associated with greater activation of bilateral orbitofrontal cortex, left occipital cortex, right precentral gyrus, and posterior cingulate, and reduced activation of dorsolateral prefrontal cortex, postcentral gyrus, and dorsal anterior cingulate gyrus. During processing of positive emotional material, estrogen administration was associated with reduced activation in the left medial frontal cortex. Taken together, there exists evidence that varying levels of estrogen are pertinent to affective processing circuitry in elder women. This relationship may be particularly relevant to elder women with MDD, who may be more vulnerable to declines in estrogen levels than elder healthy women.

Testosterone, aging, mood, and brain function. Testosterone decline has been widely shown to be associated with the aging process in men (Seidman & Walsh, 1999). Some evidence suggests that depression is associated with lower levels of testosterone in elder men (Joshi, et al., 2010; Seidman & Walsh, 1999). Exogenous administration of testosterone in men has shown some, albeit inconsistent, evidence for association with improvement in mood symptoms (Amore et al., 2012; Seidman & Walsh, 1999). As such, evidence exists that testosterone dysregulation may be a relevant neurobiological factor in elder men with depression.

Endogenous testosterone levels have been shown to be related to regulation of social emotional behavior. For example, one study (Volman, Toni, Verhagen, & Roelofs, 2011) reported that healthy young men with lower levels of testosterone had greater activation of the ventrolateral prefrontal cortex/frontal pole during an emotional control task; furthermore, lower levels of testosterone were related to greater connectivity between the amygdala and ventrolateral prefrontal cortex. Although research on the effects of testosterone upon neurophysiology in elders with MDD is lacking, preliminary evidence in healthy elder men does suggest that levels of testosterone may modulate activity of brain regions important to emotion processing. For example, Moffat and Resnick (2007) reported that in healthy elder men, higher levels of testosterone were related to greater regional cerebral blood flow (rCBF) in bilateral hippocampus, putamen, anterior cingulate gyrus, and inferior frontal gyrus, and less rCBF in the amygdala. As such, testosterone appears to exert an effect upon social and emotional behavior, in addition to the brain systems supporting emotional control; furthermore, low levels of testosterone have been associated with depression in elder men.

Taken together, the interactions between sex steroids, depression, and neurophysiology in elder men and women are not clearly elucidated, but preliminary evidence does suggest that sex

steroids may exert differential effects upon brain function in elder men and women, and these effects may be more pronounced in elders with MDD. It is possible that a subset of elder adults with MDD exhibit disrupted sex steroid regulation, which may in turn affect the functioning of brain regions supporting emotion processing. Diminished levels of these hormones from young to elder adulthood, combined with their complex interplay with the HPA axis and various mood-pertinent neurochemical systems, could contribute to the interactions between gender and age in MDD observed in the present study. Future research, integrating measurements of sex steroids, cortisol, and depression status in adults across the lifespan could elucidate these potential sex-specific mechanisms underlying the disrupted neurophysiology in chronic depression.

Emotion- and Disease-Specific regions pertinent to MDD, gender, and age group during FEP

In the present study, several regions found to vary in activation based upon MDD, gender, and age group have been previously found to be crucial to facial emotional processing, in the disease expression of MDD, and in top-down regulation of affect. The inferior frontal gyrus (IFG) in particular has been shown to be important for facial emotion processing in healthy adults (Fusar-Poli et al., 2009), aberrantly active during emotion processing in MDD (Thomas et al., 2011; van Wingen, et al., 2011), and is part of the system implicated in the pathophysiology of MDD. The IFG, particularly the right, has been demonstrated to be involved in inhibitory control (Nielson et al., 2002; Langenecker et al., 2004) and has been shown to be involved in the top-down regulation of negative emotions (Payer, Baicy, Lieberman, & London, 2012). Preliminary evidence (Briceño et al., in press) revealed that greater right versus left activation of the IFG in women with MDD was associated with increased accuracy in facial emotion processing, suggesting that among women with MDD, the IFG may play a compensatory or supplementary role in emotion processing.

The middle and superior frontal gyri have been implicated in facial emotion processing in healthy adults (Fusar-Poli, Placentino, Carletti, Allen, et al., 2009; Fusar-Poli, Placentino, Carletti, Landi, et al., 2009) and in inhibitory control (Corbetta & Shulman, 2002; Langenecker, et al., 2007). The superior frontal gyrus has been shown to be involved in regulating negative affect (Mak, Hu, Zhang, Xiao, & Lee, 2009). Given the activation patterns in these regions observed in the present findings, it appears that young women with MDD may be engaging these regions to a greater extent in an effort to regulate negative affect; men, in contrast, fail to engage these regions.

The cingulate gyrus has been shown to be involved in facial emotion processing (Fusar-Poli et al., 2009). Increased activation of the middle cingulate has been demonstrated in individuals at risk for MDD during inhibition of negative affective material (Lisiecka, et al., 2012). The middle cingulate is also implicated in the default-mode network: a group of regions that is more active during rest than during performance of cognitive tasks, which may reflect self-referential processing (Drevets, Price, & Furey, 2008).

The putamen has also been shown to be involved in facial emotion processing (Fusar-Poli et al., 2009; Wager et al., 2003). Some evidence suggests that the basal ganglia respond particularly to positive-valenced emotions (Phan et al., 2002). It has been hypothesized that the basal ganglia are involved in preparing for and coordinating responses to emotional stimuli.

Overall effect of MDD status

When the overall effect of MDD status was evaluated across men and women, young and old adults combined, only one area of activation differed between groups with and without depression, located within the precuneus. This difference was driven by deactivation of the precuneus for the MDD group during facial emotion processing (relative to processing non-

emotional, animal material), with minimal differential use of this region for the HC group. Equivalent activation within the precuneus was observed across gender and age, which suggests that the mechanism underlying the distinction from healthy adults is general to MDD. The precuneus is involved in visual-spatial processing, imagery, and sensory awareness (Cavanna & Trimble, 2006). The lateral precuneus has been demonstrated to be a part of the task positive, or attentional network (i.e., disengaged during rest and engaged during task). Individuals with MDD and their healthy counterparts may exhibit engagement of this region during processing of emotional and non-emotional visuospatial stimuli). However, among people with MDD, the introduction of emotional salience may serve to interfere with the ability to engage the attentional network, resulting in disengagement of this region during emotion processing.

The disengagement of the lateral precuneus and potentially other parts of the network activated during emotion processing might explain why performance is diminished in MDD. Diversion of resources and network attention to emotion, salience, and self-referential networks in MDD might diminish capacity for intact performance through co-engagement of the task positive, attentional network.

Given the multiple interactions between gender, age, and MDD status, the lack of robust differences between the MDD and healthy adults is not surprising. The most important implication of this finding is that evaluation of brain activation during emotion processing without accounting specifically for age and gender served to mask important networks pertinent to emotion processes in MDD. Because null findings are infrequently published, it is unclear how frequently this same pattern may have occurred in prior investigations. Indeed, the inclusion of disproportionally few men and elder adults into studies of emotion processing in MDD could be responsible for some proportion of the discrepancies in prior literature, in which some studies

report hyperactivation (e.g., Briceño et al., in press), others report hypoactivation (e.g., Lawrence et al., 2004), and others report some combination of differences compared to healthy controls (e.g., Surguladze et al., 2005; Frodl et al., 2009).

The heterogeneity of the MDD syndrome is a complex, challenging issue for researchers. Extant research has acknowledged that factors such as disease severity, illness chronicity, presence of psychiatric comorbidities, medication status, and other clinical factors are potential complicating characteristics in interpreting findings within and across studies. The present study provides compelling evidence that gender and age must also be seriously considered when conducting these studies, and may be one explanatory factor in the heterogeneity of findings with regard to the pathophysiology of MDD. This is particularly true of adult studies that include young and old participants within the same sample, such as those with ages ranging between 18 and 65. The effects in adults 55 and older appear to be opposite their younger counterparts, possibly diminishing true effects that might be related to MDD.

The present results support the notion that MDD represents an amalgam of distinct disease processes. MDD is heterogeneous classification, without an assumption regarding underlying pathology. MDD is known to be heterogeneous with regard to clinical features, with variability in symptoms, course, and treatment response. The present data also add to the literature indicating its heterogeneity with regard to neurobiology. Identification of more homogenous subtypes, with associated clinical features, genetics and neurobiological correlates, has the potential for great impact upon improved treatment success. It should be emphasized, however, that identification of more homogenous MDD subtypes is unlikely to map directly onto gender and age group categories. An improved understanding of *what about* gender and the aging

process may affect emotion processing networks in depression will be an invaluable step towards better understanding distinct neurobiological underpinnings underlying the MDD syndrome.

Effect of gender on FEP circuitry

Within healthy adults, women exhibited greater activation than men in an area that incorporated the parahippocampal gyrus, fusiform and culmen. When the investigation of the effects of gender were expanded to include adults with MDD (i.e., effect of gender within the entire sample), results were globally consistent with the results confined to healthy adults, with greater activation in women than men in the fusiform and middle temporal gyrus. These findings are consistent with prior research (e.g., Aleman & Swart, 2008), which reported increased activation in women compared to men in bilateral parahippocampal gyri during processing of facial expressions of disgust. Wager et al. (2003), in a meta-analysis, found that although men and women both activated limbic areas during facial emotion processing, peak activation localization was different between men and women, with one of the peaks in women localized to the parahippocampal cortex. They also found that men exhibited greater activation than women in the left parahippocampal gyrus/amygdala. One meta-analysis (Fusar-Poli et al., 2009) found that men exhibited greater activation than women in the right amygdala and parahippocampal gyrus. This discrepancy may be attributable to variability in the age of the sample or differences in paradigm design. However, they converge to suggest gender differences in activity in this region during affective processing.

The fusiform and parahippocampal gyrus are important in facial emotion processing (Fusar-Poli et al., 2009), involved in detection and encoding of facial information (Adolphs, 2002). As women have been typically demonstrated to exhibit more accurate processing of facial emotion than men, greater activation in this region may reflect more efficient processing of facial

information in women than in men. Supporting this hypothesis, activation of fusiform and amygdala has been shown to be positively related to accuracy in facial emotion processing in healthy adults (Loughead, Gur, Elliott, & Gur, 2008). The fusiform gyrus has been demonstrated to be involved in fine-grained analysis of visuospatial information, particularly faces (Haxby et al., 2000). As women have been demonstrated to be more efficient in facial emotion processing than men, greater fusiform involvement in women may reflect women's superior ability to detect more subtle features or differences in facial characteristics than men. Supporting this hypothesis, women have been shown to exhibit better memory for faces than men, and better discrimination of faces than men (e.g., Megreya, Bindemann, & Havard, 2011).

The finding of a single cluster associated with a gender difference in healthy adults is also in contrast to prior studies (e.g., Wager et al., 2003; Hall et al., 2004; Aleman & Swart, Kempton et al., 2009), which have reported more extensive gender differences. It is possible that the present study was underpowered to detect interactions between age and gender among the healthy adults, and that combining the sample across age obscured overall gender differences. Contrary to findings reported in prior literature, including a meta-analysis (Wager et al., 2003), there were no gender differences with regard to laterality of emotion processing circuitry: both men and women exhibited left-lateralized activation during facial emotion processing. Some evidence suggests that gender differences in lateralization depend on the valence of the emotion expressed (Killgore & Yurgelun-Todd, 2001; Lee et al., 2002). The present study incorporated both negative and positive stimuli, which may have obscured nuanced gender differences in laterality. Greater right-lateralization of facial emotion processing previously reported for healthy young men may thus depend on emotional valence. Alternatively, greater right lateralization may depend upon task difficulty: Men have been shown to be less efficient than

women in facial emotion processing, and negatively-valenced emotional expressions typically are associated with poorer accuracy than positive emotions (e.g., Wright et al. 2009). Thus, perhaps recruitment of right hemisphere resources increases with task difficulty, which occurs more frequently in men than in women. Finally, combining the age groups may have obscured a young-adult-specific lateralization effect.

Age difference in facial emotion processing

The present findings are consistent in pattern and magnitude of findings reported by prior studies (e.g., Gunning-Dixon et al., 2003) regarding differences between young and elder healthy adults in the brain areas supporting facial emotion processing; however, the subset of only healthy adults did not provide sufficient power to yield a statistically significant result. However, when examining the entire sample (including adults with MDD) age differences did reach that criterion in four regions, including the inferior frontal gyrus, lingual gyrus, cuneus, and cerebellum. Of note, the magnitude of these differences (medium to large effects) were similar in the full sample and in the healthy control group alone, indicating that the absence of a formal age effect in the healthy control group was due to insufficient power. As such, differences with regard to age in activation appear to be present in healthy adults, but were not large enough to be detected with the statistical power in the present study.

The effects of age included greater activation in young as compared to elder adults in the inferior frontal gyrus, lingual gyrus, and cerebellum. Differential activation of the prefrontal cortex in young and elder adults has been reported in prior studies of facial emotion processing. Gunning-Dixon et al. (2003) reported bilateral engagement of the inferior frontal gyrus in elder adults, with only engagement of right IFG in young adults during facial emotion processing (positive/negative emotion; old worse than young). Tessitore et al. (2005) reported increased

activation in elders compared to young adults in the ventral PFC (albeit a different cluster than that reported here). With regard to the cuneus, Gunning-Dixon et al. (2003) reported bilateral engagement of the cuneus in young, but not elder, adults. Decreased regional cerebral blood flow has been reported in the cuneus in elder adults (Asllani, et al., 2009). The cerebellum is involved in a number of cognitive processes, including affective processes (O'Halloran, Kinsella, & Storey, 2012) and has been shown to be involved in facial emotion processing (Critchley, et al., 2000). The vermis, in particular, has been implicated in involvement in regulating affective behavior (Hernaez-Goni, Tirapu-Ustarroz, Iglesias-Fernandez, & Luna-Lario, 2010). Cerebellar vermis volumes have also been shown to decline with healthy aging (e.g., Raz, Torres, Spencer, White, & Acker, 1992). Fusar-Poli et al. (2009) reported increased activation in the tuber of the vermis in old as compared to younger adults.

The direction of the age difference in these regions (i.e., greater activity in young as compared to old) was influenced by greater activation in the control condition (animal identification) task in elder compared to younger adults. Essentially, elder adults showed relatively greater activation processing identification of animals and (a relatively easy task) and relatively less activation processing facial emotion (a relatively demanding task). This pattern of response to challenge is consistent with the sigmoidal shape of the recruitment hypothesis (Rypma & D'Esposito et al., 1999; Reuter-Lorenz et al; 2005). Future studies aiming to elucidate networks involved in age differences in facial emotion processing would benefit from the use of parametric tasks in which task difficulty can be manipulated and equated between groups.

Age and gender interactions in facial emotion processing

In the present study, there was no interaction between gender and age in healthy adults. When the MDD group was included in the analysis, gender by age interactions were revealed in

middle frontal, precentral gyrus, insula, and pulvinar. Within each of these regions, activation was greater in young women compared to young men, and reduced in old women compared to old men. As with the finding regarding the overall effect of gender, it is possible that the present study was underpowered to detect interactions between age and gender among the healthy adults. However, in this case, the magnitude of the gender effects were smaller when these regions were evaluated in the healthy control group only, suggesting that the gender by age interactions were driven by inclusion of those with MDD. Indeed, activation in the middle frontal gyrus was marked by an interaction between MDD, gender, and age group: the interaction was driven by a gender by age group interaction in the MDD group (young women with MDD greater than young men with MDD, with no such difference in the elder MDD group) and a MDD status by gender interaction in the young adult group (young women with MDD greater than HC women; no such difference in men).

When evaluating the effects of age within frontal and limbic regions in healthy men and women separately, age differences were observed. Young women exhibited greater subgenual cingulate and parahippocampal gyrus/amygdala activation compared to elder women, and elder women exhibited greater bilateral dorsal anterior cingulate activation as compared to young women. The subgenual anterior cingulate has been shown to be involved in production and automatic regulation of affect (Phillips et al., 2003). This region of the anterior cingulate gyrus has been shown to decline in volume with healthy aging (e.g., Mann, et al., 2011), and women have been shown to exhibit larger volumes of this area than men (Mann et al., 2011). The parahippocampal gyrus/amygdala has been heavily implicated in its involvement in facial emotion processing (e.g., Adolphs et al., 2002; Gur et al., 2002), particularly with regard to its role in encoding and detection of emotional salience (Phillips et al., 2003). The dorsal anterior

cingulate has been shown to be involved in effortful regulatory aspects of affect (Phillips et al., 2003). As such, young women exhibited greater activation than elder women in areas important to more automatic, affect expression-pertinent regions, whereas elder women exhibited greater activation than younger women in an area pertinent to effortful affect regulation. In one study, aging was related to greater emotional stability and greater medial prefrontal control while viewing emotional images (e.g., Williams et al., 2006). The present study is generally consistent with these results, in which elder women demonstrate a pattern of increased activation in an area involved in effortful regulation combined with decreased activity of areas involved in automatic affective processing.

Younger men exhibited greater activation in a cluster incorporating the IFG and insula compared to elder men, and elder men exhibited greater activation in the bilateral parahippocampal gyrus compared to younger men. As previously reviewed, the IFG is critical to facial emotion processing (e.g., Gur et al., 2002), inhibitory control (Langenecker et al., 2007), and in affect regulation (Hariri et al., 2000). One report (Keightley, Chiew, Winocur, & Grady, 2007) found increased recruitment of the IFG in elder adults during identification of neutral and negative facial expressions. Another study (Winecoff, LaBar, Madden, Cabeza, & Huettel, 2011) reported decreased activation of the left IFG in elder compared to younger adults during conscious regulation of affect. Takahashi et al. (2011) reported greater decline in IFG volume in elder men than elder women. The insula has been implicated in the processing of emotion in faces (Haxby et al., 2000). Phan et al. (2002) suggested that the insula is particularly involved in the evaluative or experiential aspects of emotion. Insula volume has been shown to decline with age in both men and women (e.g., Takahashi et al., 2011). Elder adults have been shown to exhibit greater insula activity than young adults in response to facial emotion processing

(Keightley et al., 2007). Fusar-Poli et al. (2009) reported greater activation of the parahippocampal gyrus in old as compared to younger adults in their meta-analysis of facial emotion processing. As such, elder men exhibited greater activation than younger men in regions pertinent to evaluative and regulatory aspects of emotion, whereas younger men exhibited greater activation than elder men in a region more implicated in encoding and attending to affective information.

Overall, these different patterns between men and women in age differences during facial emotion processing could be explained gender-differential neurochemical processes as mediated by differences in sex hormones (e.g., Smith and Zubieta, 2001), differential structural decline with age (e.g., Asllani, et al., 2009; Takahashi, Ishii, Kakigi, & Yokoyama, 2011), or by differential use of affect regulation strategies (e.g., Ochsner, et al., 2004). The present data are inconclusive with regard to these underlying mechanisms, but they underscore the importance of future research to better elucidate these mechanisms.

Limitations/Future research directions

There were a number of limitations to the present study. First, although the present sample size was substantially larger than that which is typical for fMRI studies, the number of participants in each subgroup was modest. Replicating these results with a larger sample would provide additional power to pursue more nuanced lines of inquiry within this area. Second, this sample was composed of individuals with MDD with varying degrees of disease severity, illness chronicity, and psychiatric and medical comorbidities. Although this is a limitation with regard to homogeneity of the sample, this heterogeneity reflects the typical expression of MDD illness within the population (APA, 1994). Due to the limited sample size, it was impossible to conclusively rule out the contributions of each of these individual characteristics to activation

differences. However, post hoc analyses suggested that these characteristics did not drive these results. Finally, evaluation of the control condition revealed that group differences were present in the control condition. With the exception of age effects, analysis of group differences in this task compared to the group differences in the affective processing task revealed little overlap in activation, suggesting that differences in the control task did not drive the differences in activation for affective processing reported here.

Conclusions and implications.

The present study is the first to demonstrate gender differences in disrupted emotion processing circuitry in MDD, age differences in disrupted affect processing in MDD, and interactive effects with regard to both gender and age in affect processing in MDD. These findings appear independent of extraneous clinical factors, such as disease severity, medication status, and presence of medical comorbidities. These findings have critical implications for future research efforts in neurobiological processes in MDD. First, gender and age must be carefully evaluated when conducting studies of MDD, with attention to either balancing and evaluating gender and age effects within samples, or utilizing more homogenous samples (e.g., exclusively women; exclusively young). Second, future research efforts should be directed towards better understanding the mechanisms underlying these activation differences between men and women with MDD. This type of research sheds light onto the striking gender differences in the prevalence of MDD, towards enhanced understanding of the heterogeneity of MDD expression, and towards better targeting of treatments for MDD and related disorders.

APPENDIX A

Table 1. *Summary of Studies Investigating Facial Emotion Processing and Functional Neuroimaging, by Age, Gender, and Depression Status*.

	Control				*Depressed*			
	Young		*Old*		*Young*		*Old*	
Study	*Women*	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*	*Men*
Almeida et al. (2010)[1]	12	(2)			13	(2)		
Almeida et al. (2009) [1]	12	(4)			13	(2)		
Briceno et al. (in press)	22				24			
Fu et al. (2004) [1]	11	(8)			15	(6)		
Fu et al. (2007, 2008) [1]	11	(8)			13	(6)		
Lee et al. (2008) [1]	13	(2)			18	(3)		
Matthews et al. (2008)	10	(6)			12	(3)		
Thomas et al. (2011)	23	(12)			21	(7)		
Van Wingen et al. (2011)	17	(13)			25	(11)		
Dannlowski et al. (2008)	28				28			
Frodl et al. (2009)	12				12			
Lawrence et al. (2004)	11				9			
Sheline et al. (2001)	11				11			
Surguladze et al. (2005)	14				16			
Suslow et al. (2010)	26				30			
Aleman et al. (2008)	8	8						
Derntl et al. (2009)	25	25						
Hall et al. (2004)	8	8						
Kempton et al. (2009)	34	40						
Killgore et al. (2001)	6	7						
Lee et al. (2002)	12	12						
Fischer et al. (2005)	24		16					
Gunning-Dixon et al. (2003)	8		8					
Iidaka et al. (2002)	12		12					
Tessitore et al. (2005)	6	6	7	8				
Gur et al. (2002)	14							
Hariri et al. (2000)	16							
Dannlowski et al. (2007)					35			
Canli et al. (2005)					16			
Costafreda et al. (2009)					26			
Keedwell et al. (2009, 2010)					12			

[1]Men were included in the study but comprised ≤ 1/3 of the depressed sample.

Table 2. *Descriptive Statistic Comparing Demographic, Medical, and Performance Characteristics for Participants with Major Depressive Disorder (n = 53) and Healthy Controls (n = 57) Grouped by Age (Young and Old) and Gender.*

	Young				Old			
	MDD		HC		MDD		HC	
	Women (n = 15)	Men (n = 12)	Women (n = 19)	Men (n = 13)	Women (n = 12)	Men (n = 14)	Women (n = 12)	Men (n = 13)
Variables	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Age[1]	29.2 (7.8)	25.5 (3.5)	26.4 (7.7)	24.0 (6.0)	64.8 (6.3)	66.0 (9.6)	69.2 (8.6)	67.1 (8.2)
Education[1]	16.2 (2.4)	16.5 (1.9)	15.9 (2.5)	15.2 (2.1)	15.4 (2.2)	16.1 (2.8)	17.1 (1.5)	16.4 (2.4)
Hamilton Depression Rating Scale[1]	17.4 (4.3)	14.8 (4.3)	0.5 (0.8)	1.2 (1.7)	16.3 (6.3)	14.7 (4.5)	0.6 (0.8)	1.2 (1.1)
Beck Depression Inventory[1]	24.3 (7.5)	24.6 (12.8)	1.2 (1.6)	3.6 (5.4)	20.9 (10.9)	22.8 (11.0)	2.3 (3.2)	3.1 (3.6)
Hamilton Anxiety Rating Scale[1]	17.3 (6.6)	16.0 (6.5)	0.4 (0.5)	1.2 (2.1)	17.8 (9.2)	11.1 (6.5)	1.8 (2.0)	1.5 (1.8)
Charlson Comorbidity Index[1]	0.0 (0.0)	0.1 (0.3)	0.0 (0.0)	0.0 (0.0)	0.2 (0.4)	0.4 (1.0)	0 (0)	0.1 (0.3)
Years of illness (MDD only)[1]	9.2 (8.8)	5.3 (1.5)	NA	NA	40.5 (12.3)	41.3 (16.9)	NA	NA
On psychotropic medication (%)	60	20	NA	NA	75	84	NA	NA
Diabetes (*n*)	0	0	0	0	0	0	0	3
Hypertension (*n*)	1	0	0	0	5	8	3	4
Sleep apnea (*n*)	0	1	0	0	2	0	0	1
Heart condition (*n*)	0	0	0	0	4	1	0	2
FEPT Task Accuracy (% correct)[2]	85.3 (7.8)	82.3 (5.6)	86.9 (5.7)	87.7 (5.9)	73.8 (9.1)	80.2 (9.4)	81.5 (8.8)	74.8(8.5)

1. All *p*s > .05: age within age group (young, old); education, Charlson; Hamilton Depression Rating Scale, Beck Depression Inventory, Hamilton Anxiety Rating Scale, and years of illness within the MDD group.
2. $F(7, 110) = 7.30$, $p < .001$. Young HC women and men > all elder groups, young MDD women > all elder groups except old MDD men, young MDD men > old MDD women, elder MDD men > elder MDD women ($p < .05$).

Table 3. *Brain Regions Significantly Associated with a Main Effect of MDD Status (MDD, Healthy Control).*

Lobe	Gyrus	BA	mm^3	x	y	z	Z
Parietal	Precuneus	7	472	20	-65	46	3.49

Table 4. *Brain Regions Significantly Associated with Main Effect of Gender in the Total Sample (N = 100).*

Lobe	Gyrus	BA	mm^3	x	y	z	Z	Group Difference	*d*	Group difference, HC Only	*d*, HC group only
Temporal	Middle temporal	19	888	-40	-42	-2	3.5	W > M	0.90	W > M	0.78
Occipital	Fusiform	19	608	-38	-73	-11	4.26	W > M	0.82	W > M	0.85

Table 5. Brain Regions Significantly Associated with Main Effect of Age Group in the Total Sample (N = 100).

Lobe	Gyrus	BA	mm^3	x	y	z	Z	Group Difference	*d*	Group difference, HC Only	*d*, HC group only
Frontal	Inferior Frontal	47	536	40	34	1	3.57	Y > O[1]	0.74	Y > O	0.56
Occipital	Cuneus/Lingual	17/18	4496	17	-79	8	7.98	Y > O[1]	0.93	Y > O	0.97
Occipital	Lingual	18	808	-13	-73	1	3.73	Y > O[1]	0.83	Y > O	0.57
Posterior	Pyramis		1192	-20	-73	-29	3.41	Y > O[1]	0.80	Y > O	0.83

Note. O = Old, Y = Young.

1. Animals condition only O > Y for all clusters.

Table 6. *Brain Regions Significantly Associated with an Interaction between MDD Status and Age Group.*

Lobe	Gyrus	BA	mm^3	x	y	z	Z	η^2
Frontal	Precentral	6	512	15	-19	59	3.63	.15
Posterior	Cerebellum; dentate		664	-15	-60	-19	3.83	.14

Table 7. *Brain Regions Significantly Associated with an Interaction between Gender and Age Group.*

Lobe	Gyrus	BA	mm^3	x	y	z	Z	η^2 Total Sample	Contrast of interest	*p*	η^2 HC only	Relevant contrast	*p*
									YW > YM	.005		YW = YM	.504
Frontal	Middle Frontal[1]	9	488	41	28	26	3.05	.10	OW ≤ OM	.091	.03	OW = OM	.377
									YW > YM	.040		YW = YM	.191
Frontal	Precentral	13/43	680	-31	-7	29	3.37	.14	OW < OM	.001	.09	OW ≤ OM	.085
									YW ≥ YM	.074		YW = YM	.493
Subcortical	Claustrum/Insula		560	-31	6	-9	3.22	.12	OW < OM	.002	.05	OW = OM	.128
									YW > YM	.023		YW = YM	.741
Subcortical	Pulvinar		3704	3	-32	16	4.15	.18	OW < OM	.001	.09	OW < OM	.010

Note. Y = Young, O = Old, W = Women, M = Men, HC = Healthy Control.

1. Significant three-way interaction, F (1, 92) = 3.99, p = .049 (detailed in Tables 10 and 11).

Table 8. *Brain Regions Significantly Associated with an Interaction between MDD status, Gender, and Age Group.*

Lobe	Gyrus	BA	mm^3	x	y	z	Z	η^2
Frontal	Cingulate/Middle frontal	32	1464	-20	20	32	3.66	.16
Frontal	Inferior Frontal	47	472	38	26	-6	3.28	.12
Frontal	Inferior Frontal	9	504	45	12	29	3.09	.12
Frontal/Subcortical	Inferior frontal/putamen	13	920	36	10	-7	3.39	.18
Frontal	Middle frontal	8	2368	24	16	36	3.90	.19
Frontal	Superior Frontal	9	616	20	39	35	3.28	.13
Limbic	Cingulate	23	1328	-4	-11	22	3.84	.17

Table 9. *Brain Regions Significantly Associated with FEPT.*

Table 9a. Brain regions significantly associated with FEPT: Healthy Control Group (n = 53)

Lobe	Gyrus	BA	mm^3	x	y	z	Z
Frontal	Inferior frontal/Middle frontal/Insula	13/47	29936	38	12	18	6.33
Frontal	Inferior frontal/Middle frontal/Insula	47	88128	-47	20	1	6.20
Frontal	Superior frontal	9	544	-13	51	32	3.28
Temporal	Fusiform		968	38	-56	-19	3.92
Temporal	Middle temporal	22	1416	45	-44	1	4.05
Temporal	Superior/Middle temporal	38	4560	38	8	-19	4.78
Occipital	Bilateral Lingual	18	824	4	-91	-10	3.75
			0	-3	-89	-8	3.53
Subcortical	Putamen/Thalamus/Parahippocampal /hippocampus/substantia nigra	28	3296	17	-15	-12	4.07

Table 9b. Brain regions significantly associated with FEPT: Young Healthy Controls (n = 30)

Lobe	Gyrus	BA	mm^3	x	y	z	Z
Frontal	Inferior frontal	47	0	-41	18	-6	4.98
Frontal	Inferior frontal/Insula/Middle frontal/Precentral/Superior frontal	13	21008	40	12	13	5.6
Frontal	Inferior frontal/Insula/Middle frontal/Superior frontal	47/	29432	-36	45	2	5.16
Frontal	Insula	13	520	-27	-29	11	3.36
Frontal	Medial frontal	6	0	-3	14	46	3.59
Frontal	Paracentral	6	472	-8	-29	65	3.33
Limbic	Cingulate	23	1608	-4	-21	23	4.88
Limbic	Cingulate	32	3280	-1	22	38	3.63
Limbic/Parietal	Cingulate/Precuneus	31/7	528	26	-42	33	3.44
Limbic	Parahippocampal	28	464	15	-13	-12	3.81
Limbic/Parietal	Cingulate/Precuneus	24/11/7	1040	15	-15	38	3.39
Temporal	Middle temporal/inferior temporal	21/37	1784	-57	-56	4	4.46
Temporal	Middle temporal		2088	45	-44	1	4.01
Temporal	Superior temporal/middle temporal	38/21	2888	36	-1	-21	3.83
Parietal	Angular	39	2776	-29	-54	30	4.48
Occipital	Lingual/Cuneus	17/18	3080	4	-91	-10	4.66
			0	-3	-89	-8	3.64
Subcortical	Thalamus; Medial dorsal nucleus		496	-8	-15	8	3.73
Posterior	Cerebellum; Inferior semi-lunar lobule		1520	15	-65	-37	3.79
Posterior	Cerebellum; uvula/pyramis		504	-15	-69	-30	3.18
Posterior	Cerebellum; nodule		488	4	-54	-29	3.01

Table 10. *Brain Regions Significantly Associated with a Main Effect of Gender within the Healthy Control Group.*

Lobe	Gyrus	BA	mm^3	x	y	z	Z
	Fusiform/Parahippocampal/Culmen		536	22	-36	-20	3.28

Table 11. *Brain Regions Significantly Different Between Young and Old Groups in Frontal and Limbic Regions, Separated by Gender.*

11a. Young Women greater than Old Women							
Lobe	Gyrus	BA	mm^3	x	y	z	Z
Frontal	Subgenual Anterior Cingulate/Caudate head	25	736	13	26	-10	3.49
Limbic	Parahippocampal, Amygdala		520	34	-7	-20	3.36
Limbic	Parahippocampal	30	512	24	-52	8	3.20
Limbic	Parahippocampal	30	464	-24	-50	9	2.95
11b. Old Women greater than Young Women							
Lobe	Gyrus	BA	mm^3	x	y	z	Z
Limbic	Dorsal Anterior Cingulate	24/6	520	-10	-1	42	3.01
		24/6	672	8	-3	47	2.90
11c. Young Men greater than Old Men							
Lobe	Gyrus	BA	mm^3	x	y	z	Z
Frontal	IFG/Insula	13	712	36	10	-7	3.16
11d. Old Men greater than Young Men							
Limbic	Parahippocampal		848	-29	-54	-10	3.53
			1144	22	-52	-12	3.50
		30	1352	-13	-38	5	3.17

Table 12. *Analyses of Variance: Clusters Significant in MDD by Gender by Age Interaction.*

Variable	*F*	*df*	*p*	η^2	Contrast	*p*
12a. Inferior Frontal Gyrus (38 26 -6)						
					DWY > DMY	.009
Age by Gender, MDD group	10.55	1, 43	.002	.20	DWO = DMO	.069
					CWY = CMY	.648
Age by Gender, HC group	3.56	1, 49	.065	.07	CWO > COM	.040
					DWY = CWY	.516
MDD Status by Age, Women	3.63	1, 48	.063	.07	DWO ≤ CWO	.057
					DMY < CMY	.010
MDD Status by Age, Men	11.43	1, 44	.002	.21	DMO > COM	.044
					DMY < CMY	.040
MDD Status by Gender, Young	4.06	1, 50	.049	.08	DWY = CWY	.509
					DMO > COM	.047
MDD Status by Gender, Old	10.40	1, 42	.002	.20	DWO < CWO	.016
12b. Inferior/Middle Frontal Gyrus (45 12 29)						
					DWY > DMY	.028
Age by Gender, MDD Group	9.76	1, 43	.003	.19	DWO < DMO	.038
					---	---
Age by Gender, HC Group	2.17	1, 49	.147	.04	---	---
					DWY > CWY	.017
MDD Status by Age, Women	8.36	1, 48	.006	.15	DWO ≤ CWO	.098
					DMY = CMY	.254
MDD Status by Age, Men	4.85	1, 44	.033	.10	DMO ≥ COM	.056
					DWY > CWY	.041
MDD Status by Gender, Young	6.03	1, 50	.018	.11	DMY = CMY	.164
					DWO = CWO	.197
MDD Status by Gender, Old	6.04	1, 42	.018	.13	DMO > COM	.035
12c. Inferior Frontal Gyrus/Putamen (36 10 -7)						
					DWY > DMY	.009
Age by Gender, MDD group	19.22	1, 43	.001	.31	DWO < DMO	.001
					CWY ≤ CMY	.085
Age by Gender, HC group	3.91	1, 49	.054	.07	CWO = COM	.284
					DWY = CWY	.144
MDD Status by Age, Women	5.82	1, 48	.020	.11	DWO ≤ CWO	.063
					DMY < CMY	.001
MDD Status by Age, Men	22.02	1, 44	.001	.33	DMO > COM	.004
					DWY ≥ CWY	.076
MDD Status by Gender, Young	10.97	1, 50	.002	.18	DMY < CMY	.007
					DWO < CWO	.036
MDD Status by Gender, Old	9.51	1, 42	.004	.19	DMO > COM	.034

(table continues…)

Variable	*F*	*df*	*p*	η^2	Contrast	*p*
12d. Middle Frontal Gyrus (24 16 36)						
Age by Gender, MDD group	29.01	1, 43	.001	.40	DWY > DMY DWO < DMO	.001 .004
Age by Gender, HC group	2.20	1, 49	.145	.04	--- ---	--- ---
MDD Status by Age, Women	18.70	1, 48	.001	.28	DWY > CWY DWO < CWO	.001 .015
MDD Status by Age, Men	5.75	1, 44	.021	.12	DMY < CMY DMO = COM	.035 .231
MDD Status by Gender, Young	12.98	1, 50	.001	.21	DWY > CWY DMY ≤ CMY	.003 .051
MDD Status by Gender, Old	10.21	1, 42	.003	.20	DWO < CWO DMO = COM	.005 .134
12e. Middle Frontal Gyrus/Cingulate (-20 20 32)						
Age by Gender, MDD group	15.48	1, 43	.001	.27	DWY > DMY DWO < DMO	.003 .021
Age by Gender, HC group	4.33	1, 49	.043	.08	CWY = CMY CWO = COM	.220 .099
MDD Status by Age, Women	16.13	1, 48	.001	.25	DWY > CWY DWO < CWO	.010 .004
MDD Status by Age, Men	5.70	1, 44	.021	.12	DMY ≤ CMY DMO = COM	.056 .165
MDD Status by Gender, Young	9.42	1, 50	.003	.16	DWY > CWY DMY < CMY	.046 .027
MDD Status by Gender, Old	8.73	1, 42	.005	.17	DWO < CWO DMO ≥ COM	.019 .091
12f. Superior Frontal Gyrus (20 39 35)						
Age by Gender, MDD group	13.70	1, 43	.001	.24	DWY > DMY DWO < DMO	.031 .005
Age by Gender, HC group	1.60	1, 49	.211	.03	--- ---	--- ---
MDD Status by Age, Women	6.18	1, 48	.016	.11	DWY ≥ CWY DO = CO	.062 .109
MDD Status by Age, Men	8.17	1, 44	.006	.16	DMY = CMY DMO > COM	.172 .011
MDD Status by Gender, Young	4.98	1, 50	.030	.09	DWY ≥ CWY DMY = CMY	.069 .189
MDD by Gender, Old	9.93	1, 42	.003	.19	DWO ≤ CWO DMO > COM	.093 .008

(table continues…)

Variable	*F*	*df*	*p*	η^2	Contrast	*p*
12g. Cingulate (-4 -11 22)						
					DWY > DMY	.014
Age by Gender, MDD group	20.31	1, 43	.001	.32	DWO < DMO	.001
					CWY < CMY	.006
Age by Gender, HC group	3.74	1, 49	.059	.07	CWO = COM	.975
					DWY > CWY	.014
MDD Status by Age, Women	16.80	1, 48	.001	.26	DWO < CWO	.002
					DMY < CMY	.008
MDD Status by Age, Men	5.51	1, 44	.023	.11	DMO > COM	.591
					DYF > CYF	.035
MDD Status by Gender, Young	13.21	1, 50	.001	.21	DMY < CMY	.005
					DWO < CWO	.004
MDD Status by Gender, Old	6.92	1, 42	.012	.14	DMO = COM	.527

Table 13. *Post hoc Analysis of Variance Testing for Interactions for Clusters Significantly Associated with Gender and Age Group in the Total Sample.*

Variable	*F(1,92)*	*p*	η^2
13a. *Main Effect of Gender*			
Fusiform gyrus			
Main effect of Gender	16.53	.001	.15
Main effect of Age Group	0.24	.625	.00
Main effect of MDD status	2.45	.121	.03
MDD by Age Group	1.51	.222	.02
Age Group by Gender	1.17	.283	.01
MDD Status by Gender	0.02	.883	.00
MDD Status by Gender by Age Group	0.05	.826	.00
Middle Temporal Gyrus			
Main effect of Gender	18.96	.001	.17
Main effect of Age Group	0.61	.436	.01
Main effect of MDD Status	0.28	.599	.00
MDD Status by Age Group	0.16	.695	.00
Age Group by Gender	0.01	.926	.00
MDD Status by Gender	0.60	.442	.01
MDD Status by Gender by Age Group	0.13	.721	.00
13b. *Main effect of Age Group*			
Inferior Frontal Gyrus			
Main effect of Age Group	12.81	.001	.12
Main effect of Gender	.03	.858	.00
Main effect of MDD Status	2.25	.137	.00
MDD Status by Age Group	.36	.548	.00
Age Group by Gender	.09	.769	.00
MDD Status by Gender	.04	.851	.00
MDD Status by Gender by Age Group	1.90	.172	.02
Cuneus/Lingual Gyrus			
Main effect of Age Group	21.19	.001	.19
Main effect of Gender	1.60	.209	.02
Main effect of MDD Status	1.91	.170	.02
MDD Status by Age Group	.00	.961	.00
Age Group by Gender	.03	.863	.00
MDD Status by Gender	.15	.700	.00
MDD Status by Gender by Age Group	.89	.348	.01

(table continues…)

Variable	*F(1,92)*	*p*	η^2
Variable	*F(1,92)*	*p*	η^2
Lingual gyrus			
Main effect of Age Group	17.84	.001	.16
Main effect of Gender	1.69	.197	.02
Main effect of MDD Status	.18	.677	.00
MDD Status by Age Group	1.90	.171	.02
Age Group by Gender	.33	.566	.00
MDD Status by Gender	.14	.711	.00
MDD Status by Gender by Age Group	.01	.933	.00
Pyramis (22 -72 -28)			
Main effect of Age Group	15.45	.001	.14
Main effect of Gender	.03	.874	.00
Main effect of MDD Status	.29	.589	.00
MDD Status by Age Group	.01	.917	.00
Age Group by Gender	.03	.870	.00
MDD Status by Gender	.06	.801	.00
MDD Status by Gender by Age Group	1.28	.261	.01

Table 14. *Post-hoc Analysis of Variance Testing Three-way Interactions for Clusters Significantly Associated with Gender by Age Group Interaction in the Total Sample.*

Variable	*F (1, 92)*	*p*	η^2
Middle frontal gyrus	3.99	.049	.04
Precentral gyrus	0.58	.450	.01
Claustrum	1.67	.199	.02
Pulvinar	2.69	.104	.03

Table 15. *Post hoc Analysis of Variance: Decomposing Three-way Interaction in the Middle Frontal Gyrus Cluster Identified in the Gender by Age Interaction in the Total Sample.*

Variable	*F*	*df*	*p*	η^2	Contrast	*p*
Middle frontal gyrus						
					DWY > DMY	.002
Gender by Age group, MDD group	11.71	1, 43	.001	.21	DWO = DMO	.143

Gender by Age group, HC group	1.24	1, 49	.271	.03		

MDD status by Age group, Women	3.65	1, 48	.062	.07		

MDD status by Age group, Men	1.10	1, 44	.300	.02		
					DWY > CWY	.046
MDD status by Gender, Young	6.01	1, 50	.018	.11	DMY = CMY	.152

MDD status by Gender, Old	0.29	1, 42	.593	.01		

APPENDIX B

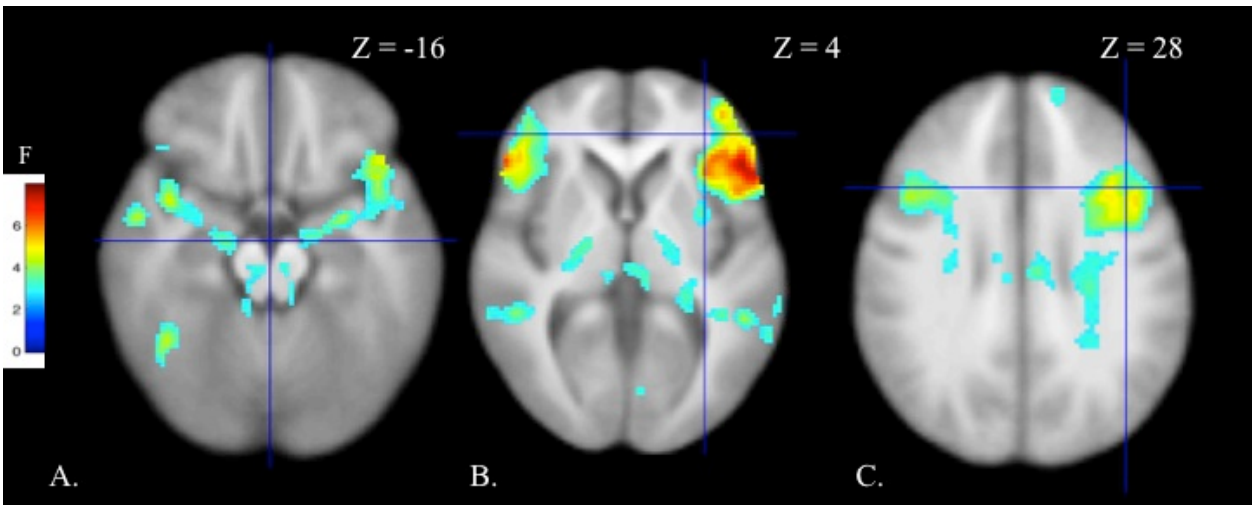

Figure 1. This figure illustrates areas of task-related activation in response to the FEPT in healthy adults. Activation is demonstrated in the bilateral hippocampus/amygdala, substantia nigra, superior temporal gyrus/uncus, and fusiform gyrus (Panel A), bilateral inferior frontal gyrus/amygdala, putamen, and thalamus (Panel B), and middle frontal gyrus/cingulate (Panel C). The z coordinate is displayed in the Talairach system; the scale displays corresponding F values.

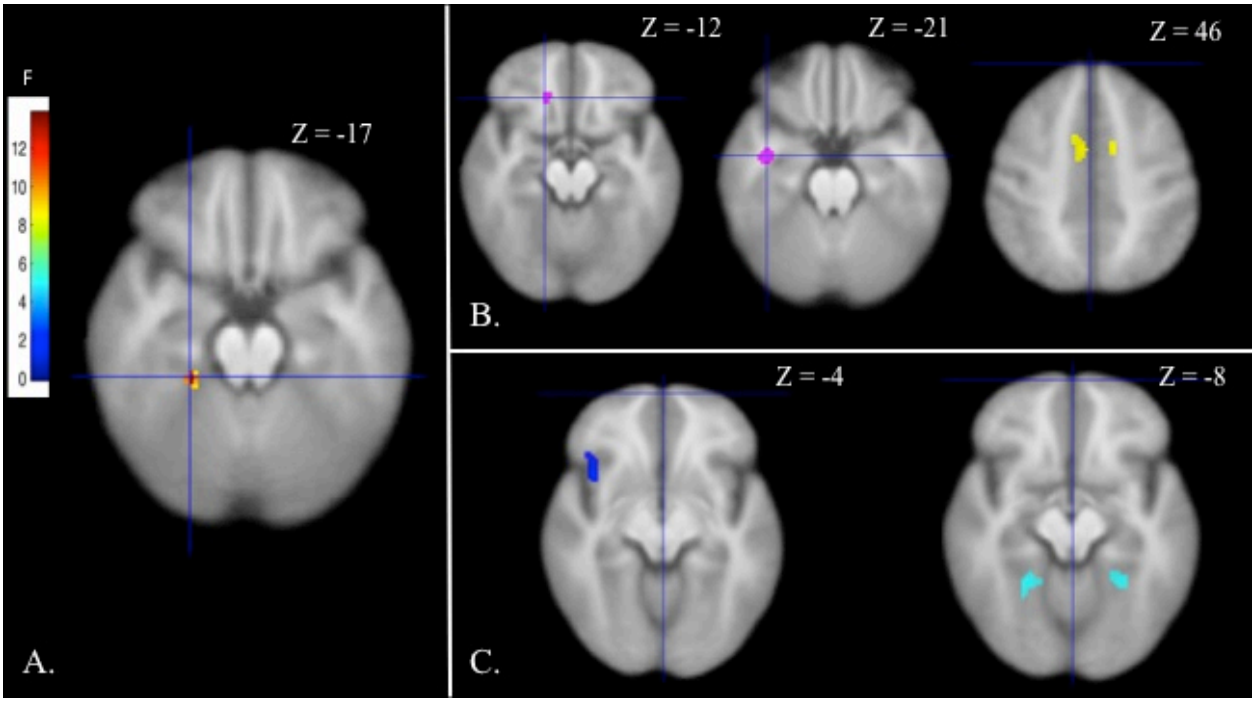

Figure 2. Panel A illustrates greater activation in healthy control women compared to healthy control men in a cluster extending to the parahippocampal gyrus, fusiform, and culmen of the cerebellum. Panel B illustrates greater activation in young women compared to old women (pink; left and middle) in the subgenual anterior cingulate and parahippocampal gyrus, and greater activation in old women compared to young women (yellow; right) in the dorsal anterior cingulate gyrus. Panel C illustrates greater activation in young men compared to elder men (blue; left) in the IFG/insula, and greater activation in elder men compared to young men (cyan; right) in the bilateral parahippocampal gyrus. The z coordinate is displayed in the Talairach system; the scale displays corresponding F values.

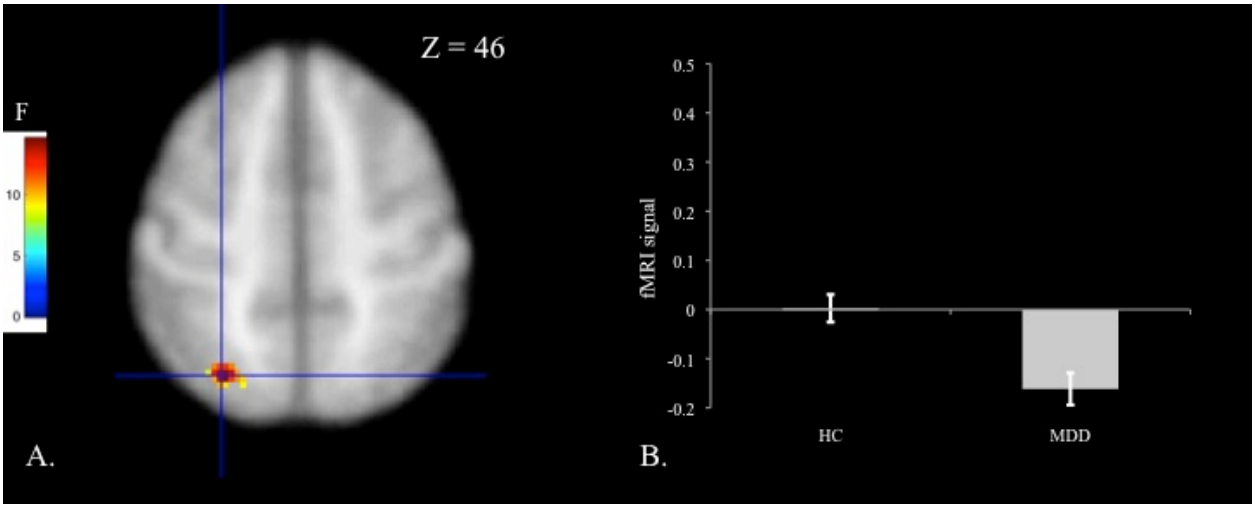

Figure 3. The figure illustrates less activation of the precuneus in the MDD group as compared to the healthy control group during facial emotion processing (Panel A). Panel B graphs task-related activation signal in the healthy control (HC) and Major Depressive Disorder (MDD) groups. The z coordinate is displayed in the Talairach system; the scale displays corresponding F values.

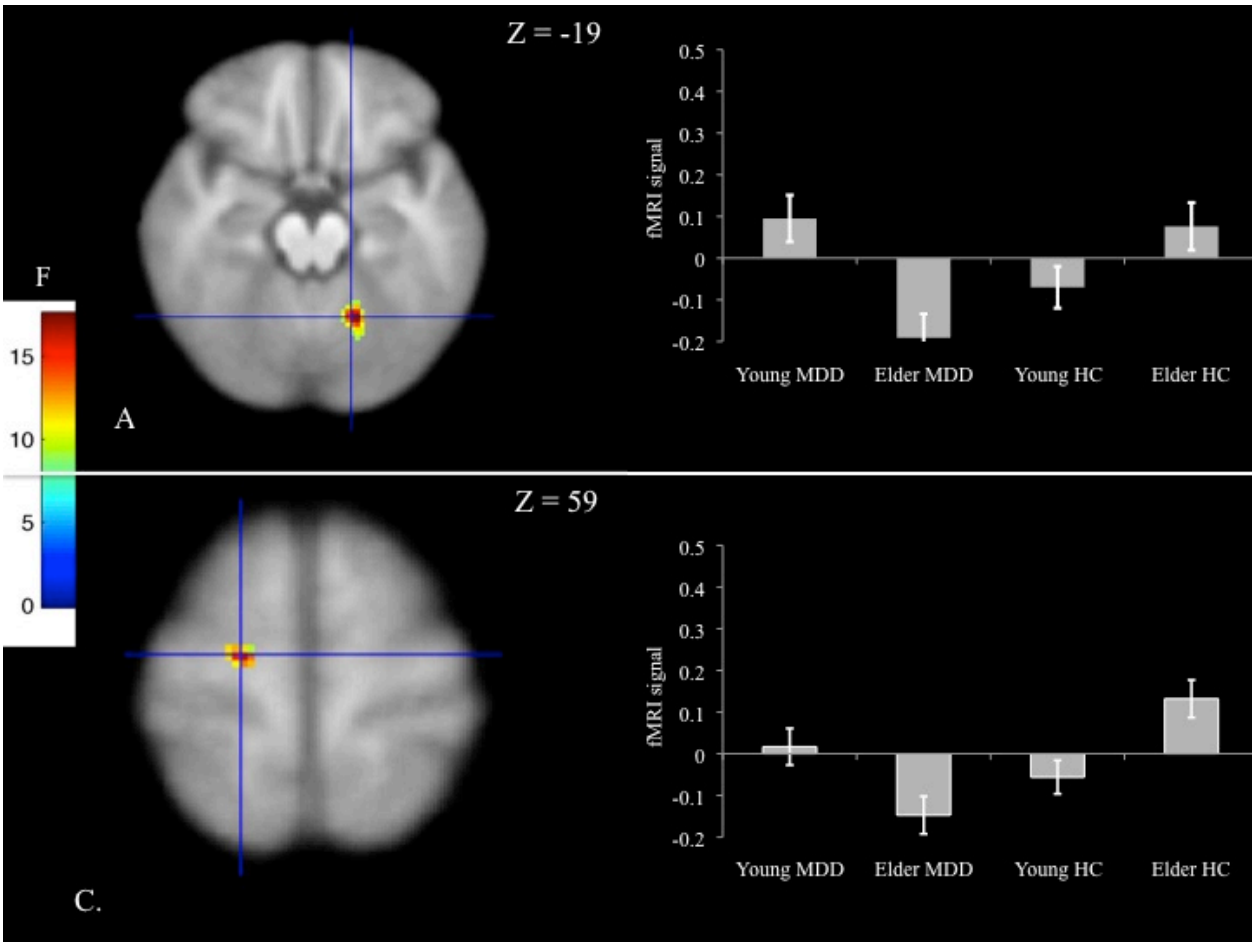

Figure 4. The figure illustrates areas significant for an MDD status by age group interaction during facial emotion processing, including the dentate of the cerebellum (Panel A) and precentral gyrus (Panel B). For the dentate, activation was greater in the MDD compared to the HC group in the young adults, and activation was reduced in the MDD compared to the HC group in the elder adults (Panel A, right). For the precentral gyrus, the MDD group exhibited reduced activation compared to the HC group in the elder group, with no significant effect of MDD in the young group (Panel B, right). The z coordinate is displayed in the Talairach system; the scale displays corresponding F values. MDD = Major Depressive Disorder; HC = Healthy Control.

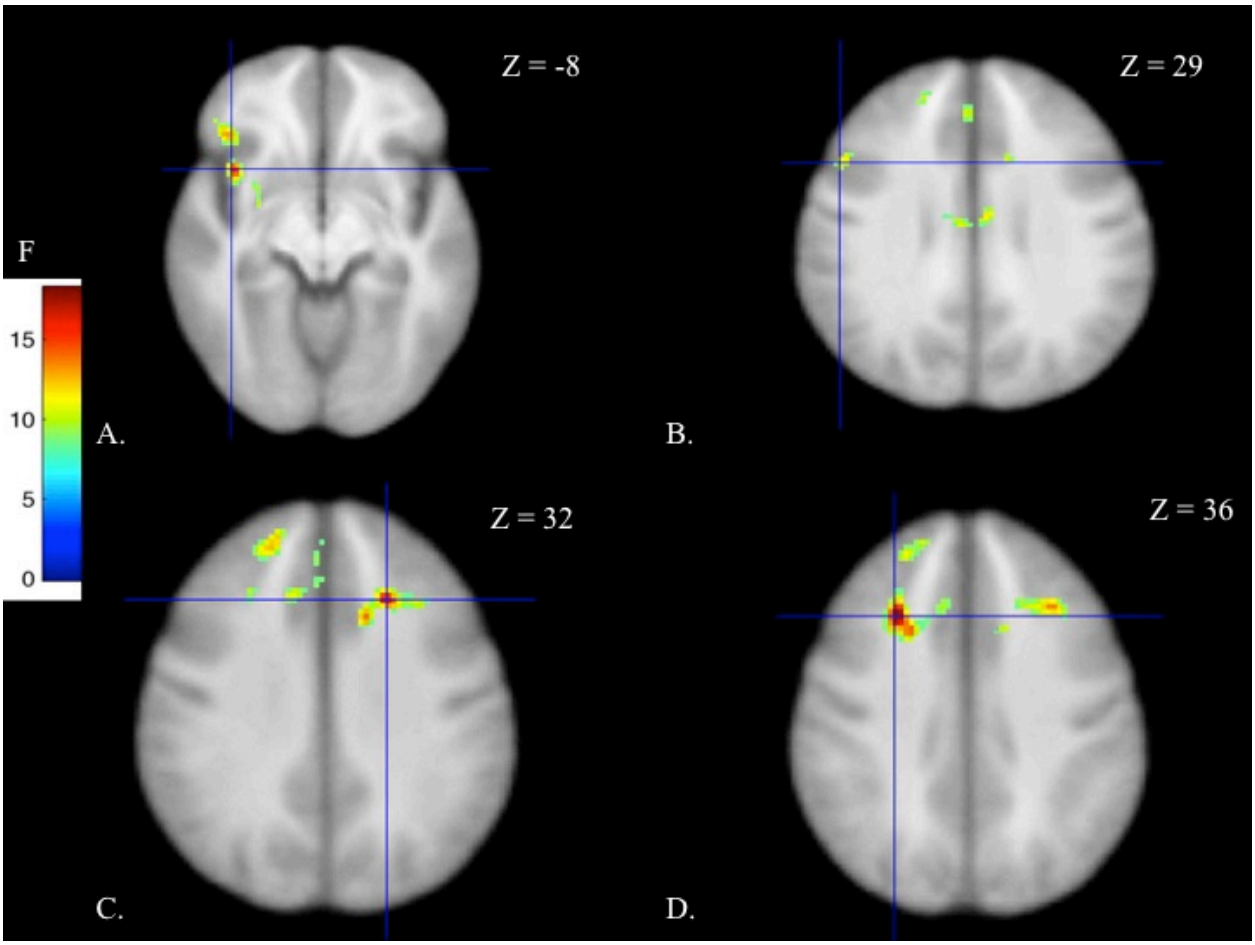

Figure 5. This figure illustrates regions significant for an interaction between MDD status, gender, and age group during facial emotion processing, including the inferior frontal gyrus and putamen (Panel A), inferior/middle frontal gyrus and cingulate (Panel B), middle and superior frontal gyri (Panel C), and middle frontal gyrus/cingulate and superior frontal gyrus (Panel D). The z coordinate is displayed in the Talairach system; the scale displays corresponding F values.

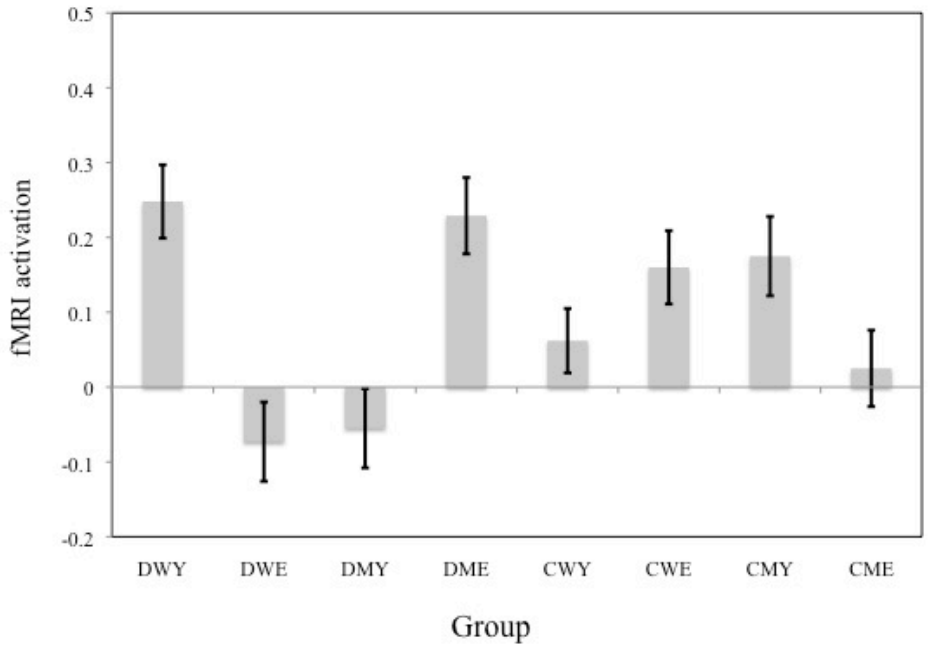

Figure 6. The figure illustrates the averaged extracted activation signal for the areas significant for an MDD status by gender by age group interaction (See Figure 5). Numbers denote decomposed two-way interactions within the three-way interaction.
Note. Group status: D = Major Depression Disorder (MDD), C = Control group; W = Women, M = Men; Y = Young, E = Elder.
1. Gender x Age, MDD: DWY > DMY, DWE < DME (Young significant for 7/7 clusters; Elder significant for 6/7 clusters)
2. MDD x Age, Women: DWY > CWY, DWE < CWE (Young significant for 4/7 clusters; Elder significant for 3/7 clusters)
3. MDD x Age, Men: (DMY < CMY, DME > CME (Young significant for 4/7 clusters; Elder significant for 3/7 clusters)
4. MDD x Gender, Young: DWY > CWY, DMY < CMY (Women significant for 4/7 clusters; Men significant for 4/7 clusters)
5. MDD x Gender, Elder: DWE < CWE, DME > CME (Women: significant for 5/7 clusters; Men: significant for 4/7 clusters)

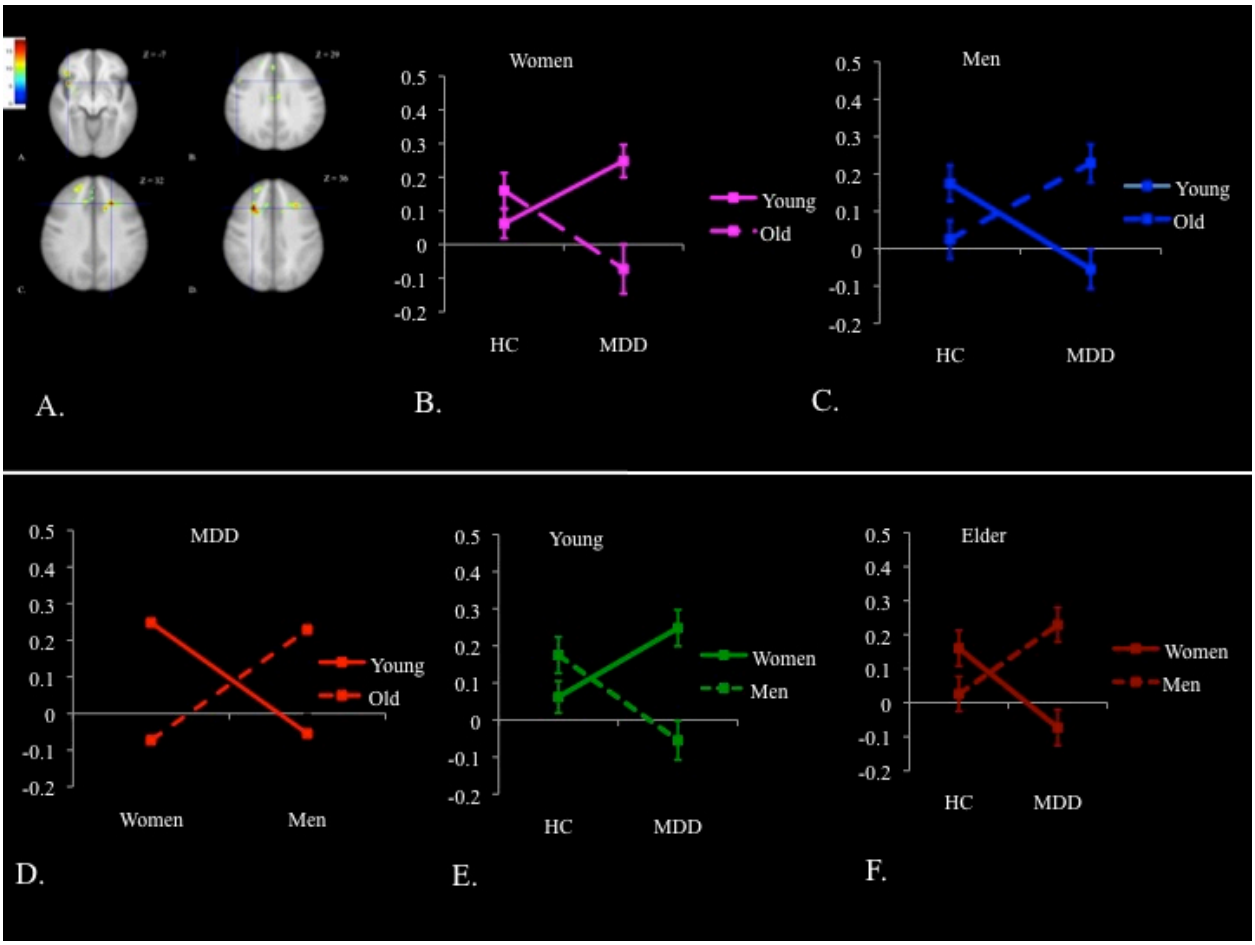

Figure 7. The figure illustrates decomposed two-way interactions for areas significant for an MDD status by gender by age group interaction (See Figures 5 and 6). Activation signal reflects averaged signal across the seven areas significant for the three-way interaction.
Note: HC = Healthy Control; MDD = Major Depressive Disorder.
A. Gender x Age, MDD: DWY > DMY, DWE < DME (Young significant for 7/7 clusters; Elder significant for 6/7 clusters)
B. MDD x Age, Women: DWY > CWY, DWE < CWE (Young significant for 4/7 clusters; Elder significant for 3/7 clusters)
C. MDD x Age, Men: (DMY < CMY, DME > CME (Young significant for 4/7 clusters; Elder significant for 3/7 clusters)
D. MDD x Gender, Young: DWY > CWY, DMY < CMY (Women significant for 4/7 clusters; Men significant for 4/7 clusters)
E. MDD x Gender, Elder: DWE < CWE, DME > CME (Women: significant for 5/7 clusters; Men: significant for 4/7 clusters)

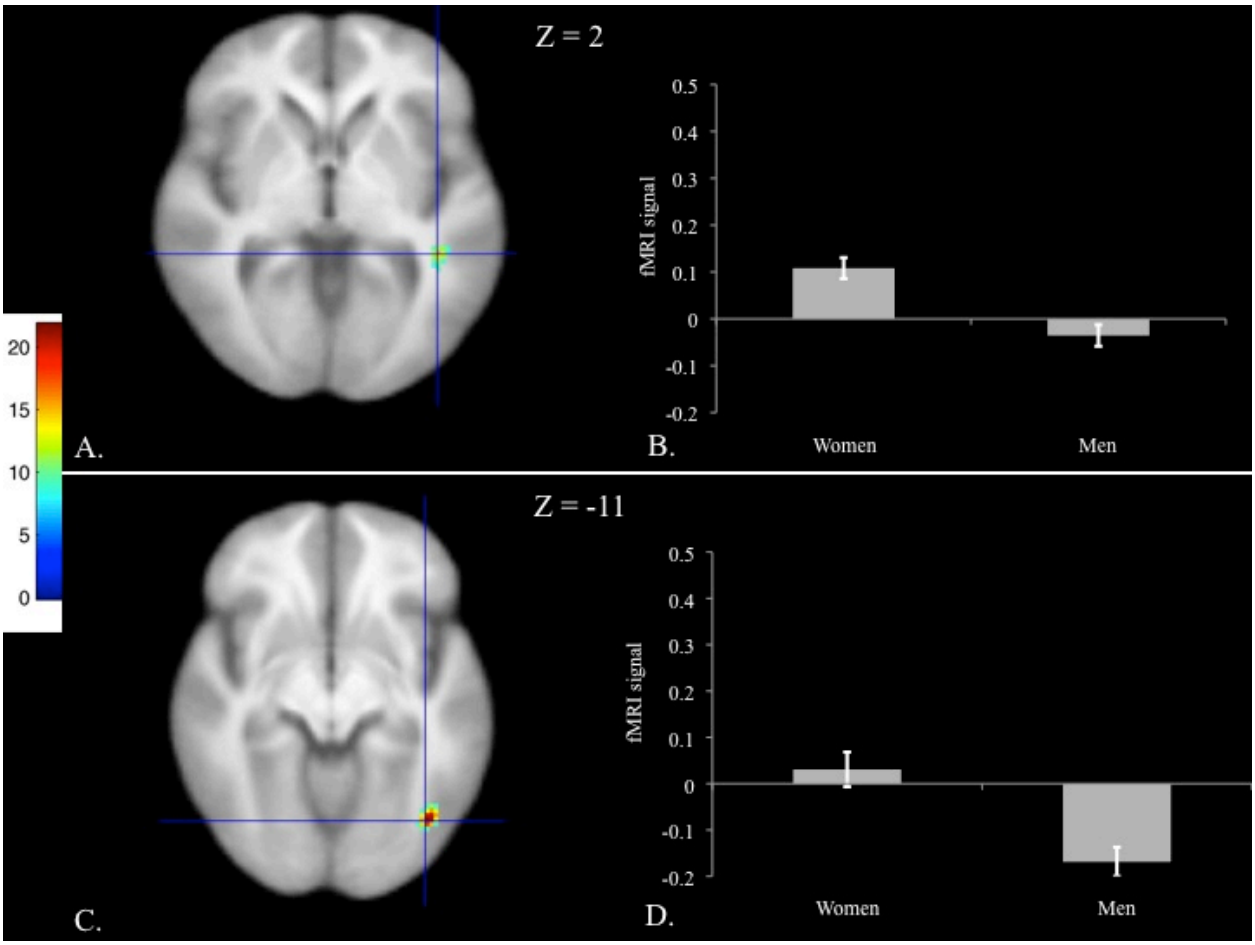

Figure 8. In the full sample including both the healthy control (HC) and Major Depressive Disorder (MDD) groups, women exhibited greater activation than men in two clusters, including the middle temporal gyrus (illustrated in Panel A; extracted signal graphed in Panel B) and fusiform gyrus (Illustrated in Panel C; extracted signal graphed in Panel D). The z coordinate is displayed in the Talairach system; the scale displays corresponding F values.

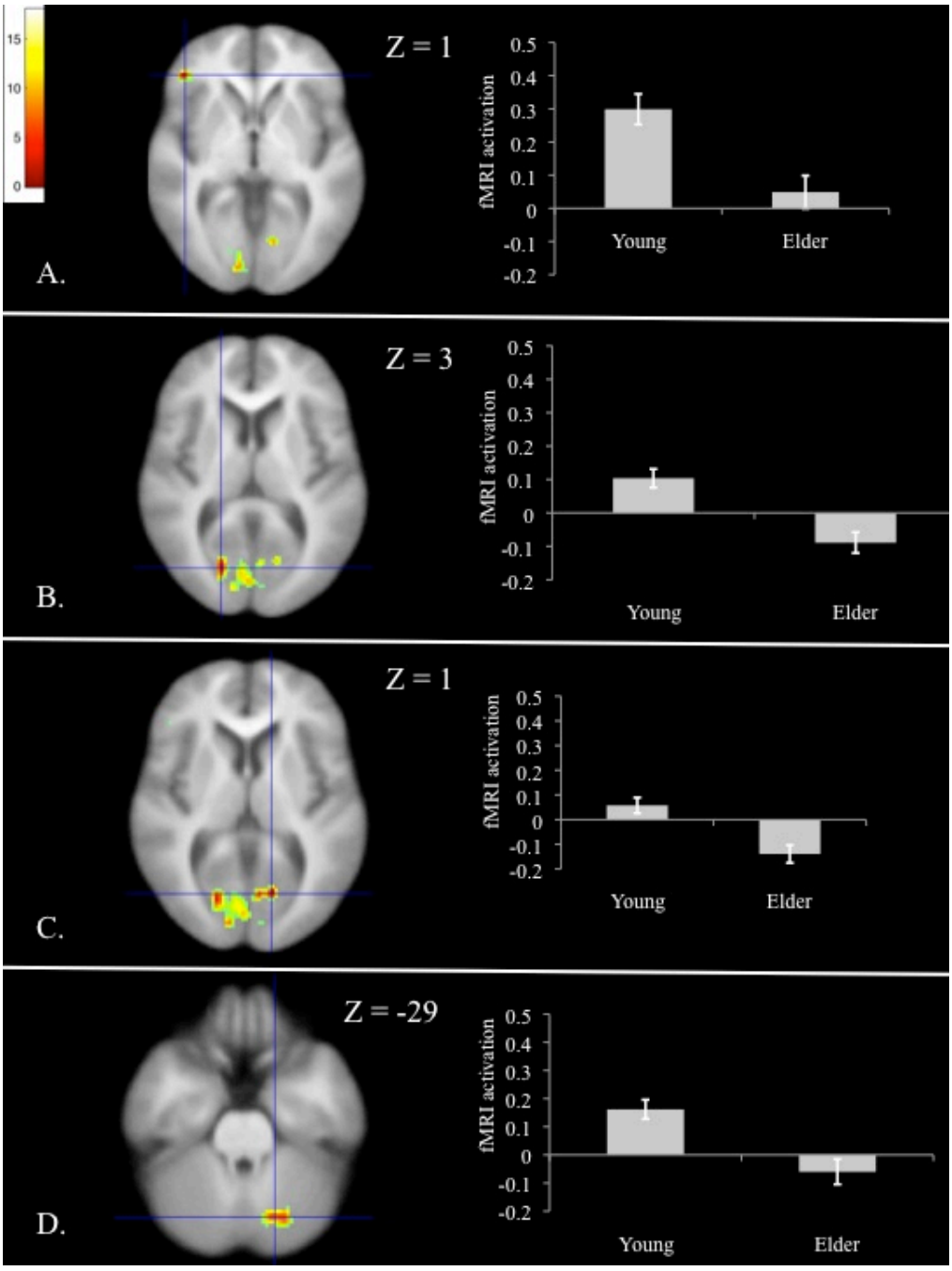

Figure 9. In the full sample including both the healthy control (HC) and Major Depressive Disorder (MDD) groups, younger adults exhibited greater activation than elders in four clusters, including the inferior frontal gyrus (illustrated in Panel A, left; extracted signal graphed on the right), cuneus/lingual gyrus (illustrated in Panel B, left; extracted signal graphed on the right), lingual gyrus (illustrated in Panel C, left; extracted signal graphed on the right), and pyramis of cerebellum (illustrated in Panel D, left; extracted signal graphed on the right). The z coordinate is displayed in the Talairach system; the scale displays corresponding F values.

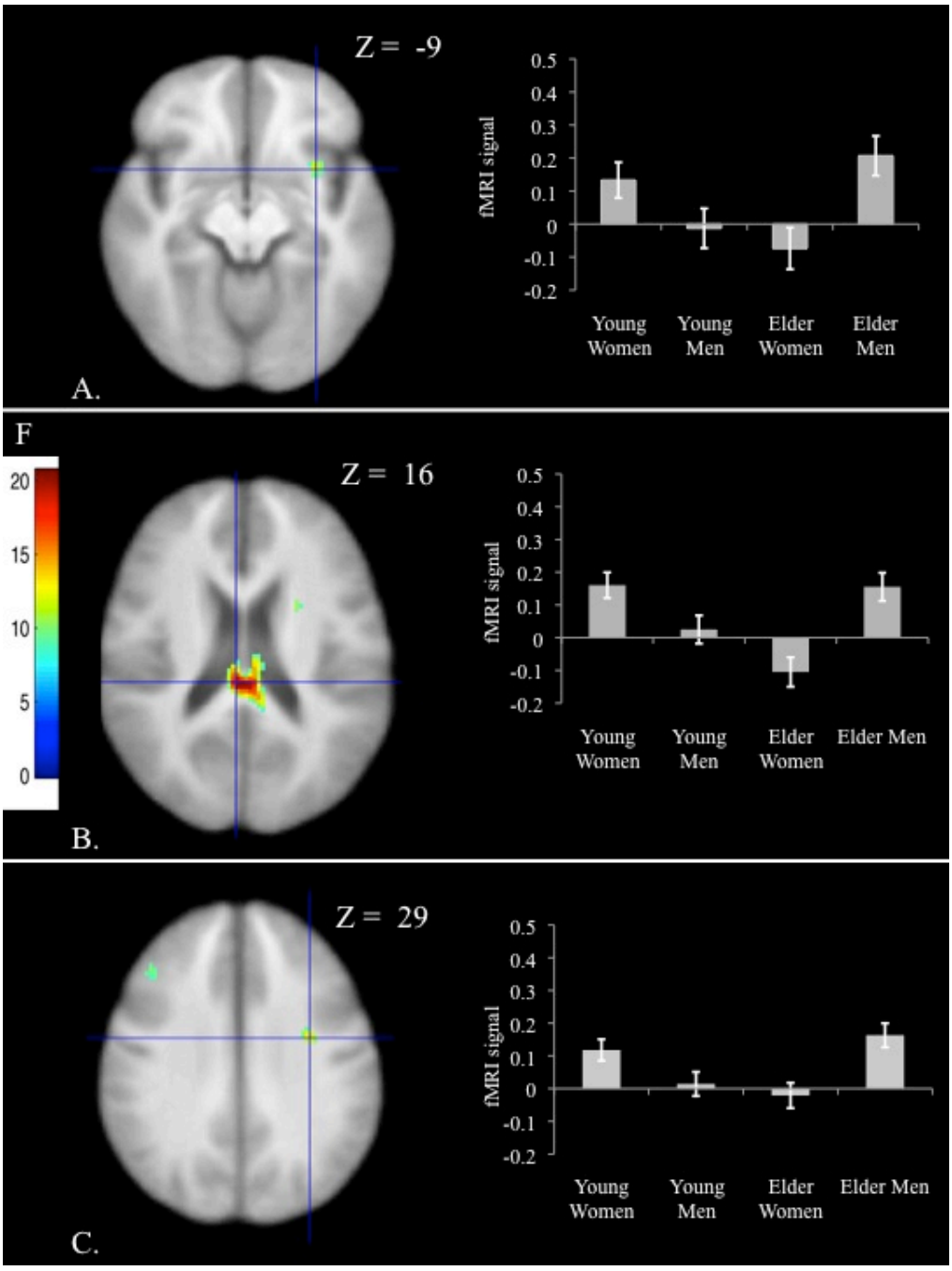

Figure 10. The figure illustrates (left) and graphs (right) areas of significant interaction between gender and age in the full sample including both the healthy control (HC) and Major Depressive Disorder (MDD) groups, including the claustrum/insula (Panel A), pulvinar (Panel B), and precentral gyrus (Panel C). The z coordinate is displayed in the Talairach system; the scale displays corresponding F values.

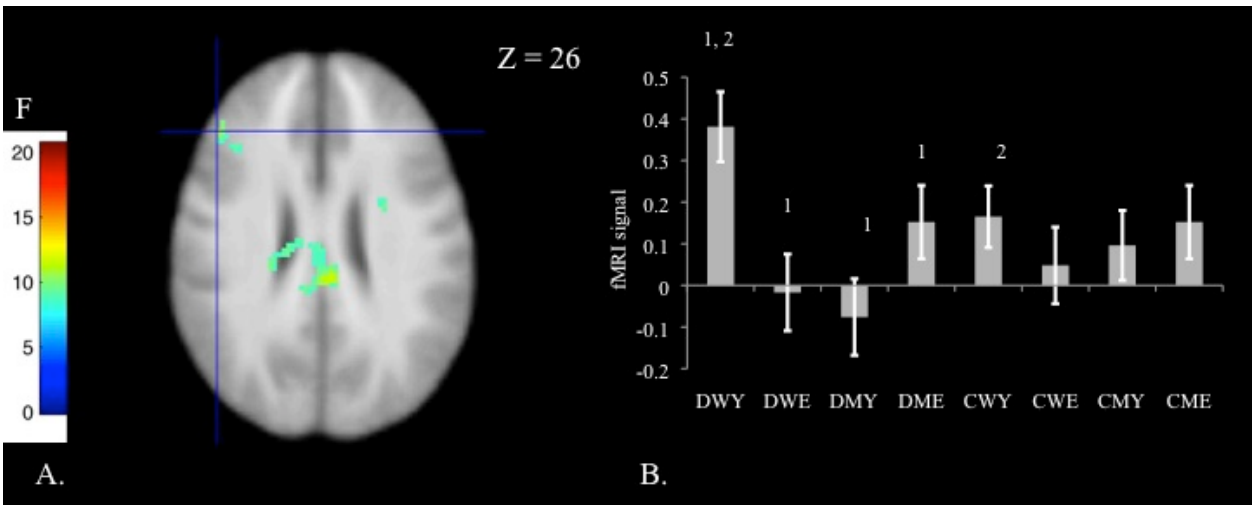

Figure 11. Panel A displays activation in the middle frontal gyrus cluster that was significant for a gender by age interaction in the full sample. Post hoc analysis revealed a significant MDD by gender by age group interaction, which is graphed in Panel B.
Note. Group status: D = Major Depression Disorder (MDD), C = Healthy Control group; W = Women, M = Men; Y = Young, E = Elder.
1. Significant for gender by age interaction in MDD group (DWY > DMY; DWE < DME)
2. Significant for gender by age interaction in young group (DWY > CWY)

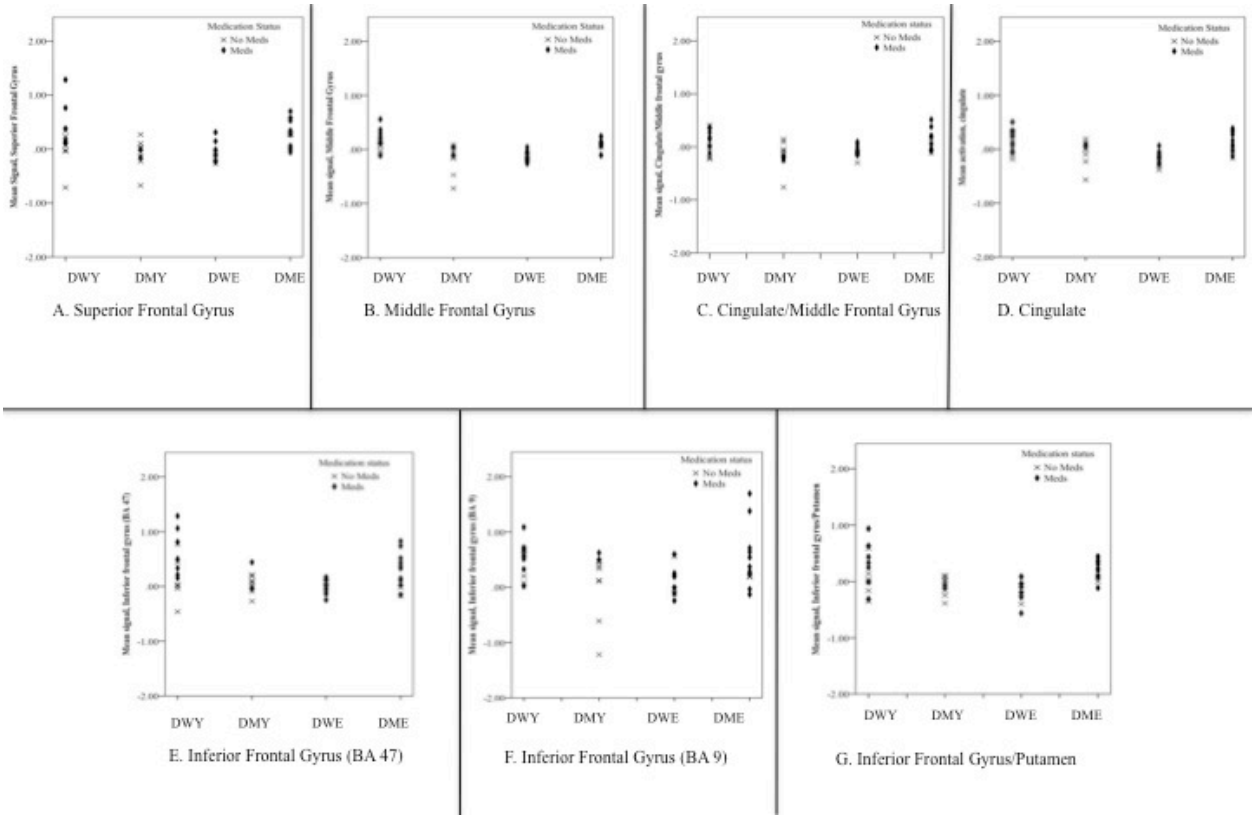

Figure 12. The figure displays scatterplots of activation for MDD subgroups separated by those taking psychotropic medications and those who were not taking psychotropic medications.

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ABSTRACT

THE INFLUENCE OF GENDER AND AGING ON THE NEURAL CIRCUITRY SUPPORING FACIAL EMOTION PROCESSING IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

by

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Major Depressive Disorder (MDD) is associated with decrements in facial emotion processing (FEP). Previous studies investigating the neural substrates of these decrements have often reported hyperactivity of emotion processing circuitry. Neural circuitry supporting FEP has been shown to be different between healthy men and women, and between young and elder adults. However, no prior studies have investigated how gender and aging affect emotion processing circuitry in individuals with MDD. The present study aimed to investigate the influence of gender and aging on emotion processing circuitry in MDD. One hundred-ten adults, grouped into subgroups according to MDD status, gender, and age group, completed a facial emotion processing task (FEPT) while undergoing functional magnetic resonance imaging (fMRI). Interactions were revealed between MDD status, gender, and age group in a number of brain regions important to emotion processing. These regions included the inferior, middle, and superior frontal gyrus, cingulate, and putamen. Within younger adults, women with MDD exhibited hyperactivation of these regions compared to healthy control (HC) women, consistent with prior research. Young men with MDD, however, exhibited hypoactivity of these same

regions compared to young HC men. Within elder adults, women with MDD exhibited hypoactivity of emotion processing regions compared to HC women, whereas men with MDD exhibited hyperactivity of these regions compared to HC men. These findings underscore the importance of attendance to these interactions in studies of emotion processing in MDD, and suggest that gender- and age- specific mechanisms underlie dysfunction in emotion processing circuitry in MDD.

AUTOBIOGRAPHICAL STATEMENT

EMILY MARIE BRICEÑO

Emily Briceño completed her Bachelor of Arts degree at Kalamazoo College, with a major in Psychology and a minor in Spanish. She completed her undergraduate thesis on the effects of aging on the neural substrates of motor control in the laboratory of Rachel Seidler, PhD, at the University of Michigan. She earned departmental honors in Psychology, and also received departmental awards for her undergraduate thesis, comprehensive examination in psychology, and psychology coursework. Following graduation, she worked as a research assistant at the University of Michigan, in the division of Neuropsychology in the Department of Psychiatry. She entered the WSU Clinical Psychology Ph.D. program in 2006. She completed her Master's thesis in 2009, investigating age-related differences in spatial navigation performance, under the supervision of Scott Moffat, Ph.D. Following completion of her Master's thesis, she initiated this collaborative dissertation project with Drs. Lisa Rapport (WSU) and Scott Langenecker (University of Michigan) with the aim of linking her interests in clinical psychology, aging, and neuroscience. She has authored or co-authored six published or in-press publications and 22 abstracts. She has conducted clinical practica in neuropsychology and rehabilitation psychology at the Rehabilitation Institute of Michigan and in neuropsychology at the Detroit Medical Center Department of Neurology. She was awarded the Norine G. Johnson Clinical Psychology award and the Gerald Rosenbaum Clinical Psychology Award within the WSU Psychology department. She is currently completing her APA-accredited internship at the Ann Arbor VA Medical Center.